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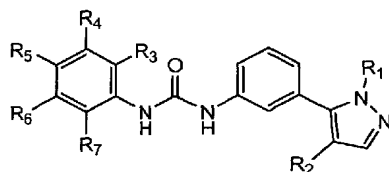
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(54) Title: PROCESS OF MAKING PHENYLPYRAZOLES USEFUL AS SELECTIVE 5HT_{2A} MODULATORS AND INTERMEDIATES THEREOF



(I)

(57) Abstract: The present invention relates to a process for making certain selective 5HT_{2A} modulators of Formula (I) and the intermediates thereof: Formula (I) wherein R₁-R₇ are described. Compounds of Formula (I) are useful in the prophylaxis or treatment of 5HT_{2A} mediated diseases, such as, 5HT_{2A} mediated platelet aggregation, asthma, agitation, degenerative diseases of the CNS and the like.

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**PROCESS OF MAKING PHENYLPYRAZOLES USEFUL
AS SELECTIVE 5HT_{2A} MODULATORS
AND INTERMEDIATES THEREOF**

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FIELD OF THE INVENTION

The present invention concerns a process for making certain selective 5HT_{2A} modulators for the 5-HT_{2A} receptor. In particular, the application concerns a process for making compounds of Formula (I), as disclosed herein below, which are useful in the prophylaxis or treatment of 5HT_{2A} mediated disorders.

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BACKGROUND OF THE INVENTION

I. G protein-coupled receptors

G protein-coupled receptors share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane. The transmembrane helices are joined by strands of amino acids having a larger loop between the fourth and fifth transmembrane helix on the extracellular side of the membrane. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly with the amino terminus in the extracellular space. It is thought that the loop joining helices five and six, as well as, the carboxy terminus, interact with the G protein. Currently, Gq, Gs, Gi and Go are G proteins that have been identified.

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Under physiological conditions, G protein-coupled receptors exist in the cell membrane in equilibrium between two different states or conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response.

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A receptor may be stabilized in an active state by an endogenous ligand or an exogenous agonist ligand. Recent discoveries such as, including but not exclusively limited

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to, modifications to the amino acid sequence of the receptor provide means other than ligands to stabilize the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

II. Serotonin receptors

Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein-coupled receptors. Serotonin is thought to play a role in processes related to learning and memory, sleep, thermoregulation, mood, motor activity, pain, sexual and aggressive behaviors, appetite, neurodegenerative regulation, and biological rhythms. Not surprisingly, serotonin is linked to pathophysiological conditions such as anxiety, depression, obsessive-compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism, and neurodegenerative disorders. With respect to an anti-psychotic treatment, approaches focused on the serotonin receptors, these types of therapeutics can generally be divided into two classes, the "typical" and the "atypical." Both have anti-psychotic effects, but the typicals also include concomitant motor-related side effects (extra pyramidal syndromes, *e.g.*, lip-smacking, tongue darting, locomotor movement, etc). Such side effects are thought to be associated with the compounds interacting with other receptors, such as the human dopamine D2 receptor in the nigro-striatal pathway. Therefore, an atypical treatment is preferred. Haloperidol is considered a typical anti-psychotic, and clozapine is considered an atypical anti-psychotic.

Serotonin receptors are divided into seven subfamilies, referred to as 5-HT1 through 5-HT7, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT2 subfamily is divided into three receptor subtypes: 5-HT2A, 5-HT2B, and 5-HT2C. The human 5-HT2C receptor was first isolated and cloned in 1987, and the human 5-HT2A receptor was first isolated and cloned in 1990. These two receptors are thought to be the site of action of hallucinogenic drugs. Additionally, antagonists to the 5-HT2A and 5-HT2C receptors are believed to be useful in treating depression, anxiety, psychosis, and eating disorders.

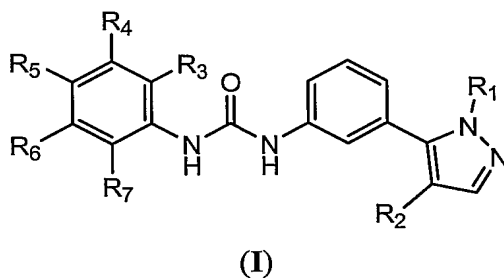
U.S. Patent Number 4,985,352 describes the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT1C receptor (now known as the 5-HT2C receptor). U.S. Patent Number 5,661,012 describes the isolation,

characterization, and expression of a functional cDNA clone encoding the entire human 5-HT_{2A} receptor.

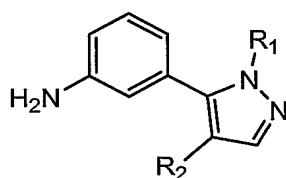
Mutations of the endogenous forms of the rat 5-HT_{2A} and rat 5-HT_{2C} receptors have been reported to lead to constitutive activation of these receptors (5-HT_{2A}: Casey, C. *et al.* (1996) *Society for Neuroscience Abstracts*, 22:699.10, hereinafter "Casey"; 5-HT_{2C}: Herrick-Davis, K., and Teitler, M. (1996) *Society for Neuroscience Abstracts*, 22:699.18, hereinafter "Herrick-Davis 1"; and Herrick-Davis, K. *et al.* (1997) *J. Neurochemistry* 69(3): 1138, hereinafter "Herrick-Davis-2"). Casey describes a mutation of the cysteine residue at position 322 of the rat 5-HT_{2A} receptor to lysine (C322K), glutamine (C322Q), and arginine (C322R) which reportedly led to constitutive activation. Herrick-Davis 1 and Herrick-Davis 2 describe mutations of the serine residue at position 312 of the rat 5-HT_{2C} receptor to phenylalanine (S312F) and lysine (S312K), which reportedly led to constitutive activation.

SUMMARY OF THE INVENTION

The present invention, in one aspect, provides a process for making compounds of Formula (I) useful in the prophylaxis or treatment of 5HT_{2A} mediated disorders, such as, 5HT_{2A} mediated platelet aggregation, asthma, agitation, degenerative diseases of the CNS, add-on therapy to Haloperidol for schizophrenia and other psychopathic disorders, as well as other diseases.

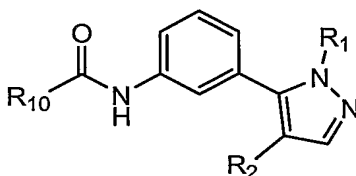


Some embodiments of the invention relate to the process for making compounds of Formula (A5) that are useful as intermediates in making compounds of Formula (I):



(A5)

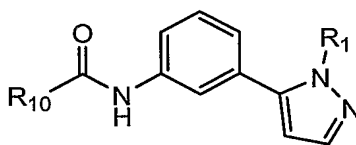
the process comprising hydrolyzing a compound of Formula (A4):



(A4)

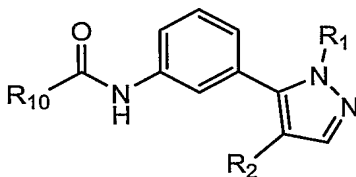
with an alkali metal hydroxide in a hydrolyzing solvent to yield a compound of Formula (A5); R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; and R₁₀ is C₁₋₆ alkyl. In some embodiments the alkali metal hydroxide is sodium hydroxide. In some embodiments the hydrolyzing solvent is aqueous ethanol. In some embodiments of the process for making a compound of Formula (A5) the hydrolyzing step is conducted between about 60°C to about 80°C.

In some embodiments the process for making a compound of Formula (A5) comprises the steps of halogenating a compound of Formula (A3):



(A3)

with a halogenating reagent in a halogenating solvent to yield a compound of Formula (A4):

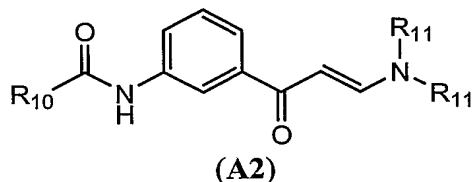


(A4)

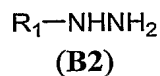
and hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5); wherein R₁₀ is C₁₋₆ alkyl. In some embodiments the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide. In some embodiments the halogenating reagent is N-

bromosuccinimide and the halogenating solvent is N,N-dimethylformamide and the halogenating step is conducted between about 20°C to about 60°C. In some embodiments of the process for making a compound of Formula (A5) the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted between about 60°C to about 80°C.

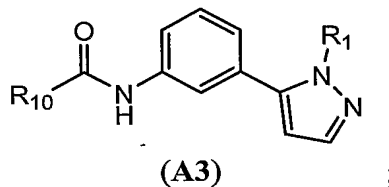
In some embodiments the process for making a compound of Formula (A5) comprises the steps of cyclizing a compound of Formula (A2):



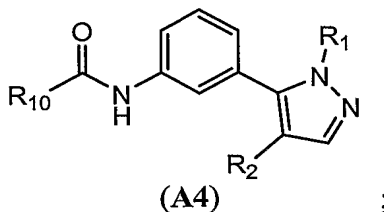
with a compound of Formula (B2):



the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (A3):



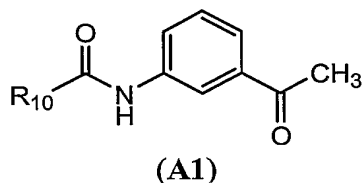
halogenating a compound of Formula (A3) with a halogenating reagent in a halogenating solvent to yield a compound of Formula (A4);



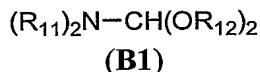
and hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5); wherein R₁ is C₁₋₂ alkyl; R₁₀ is C₁₋₆ alkyl; and R₁₁ is C₁₋₃ alkyl. In some embodiments the process further comprises a cyclizing acid in the cyclizing step. In some embodiments the cyclizing acid is hydrochloric acid. In some embodiments the compound of Formula (B2) is methyl

hydrazine. In some embodiments the cyclizing solvent is methanol. In some
embodiments the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide,
the halogenating solvent is N,N-dimethylformamide, and the halogenating step is
conducted between about 20°C to about 60°C. In some embodiments the alkali metal
hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the
hydrolyzing step is conducted between about 60°C to about 80°C.

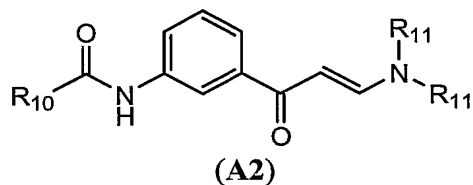
In some embodiments the process for making a compound of Formula (A5)
comprises the steps of condensing a compound of Formula (A1):



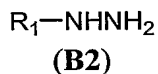
with a compound of Formula (B1):



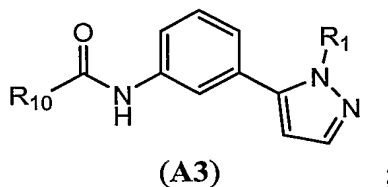
the condensing step is optionally conducted in an condensing solvent to yield a
compound of Formula (A2):



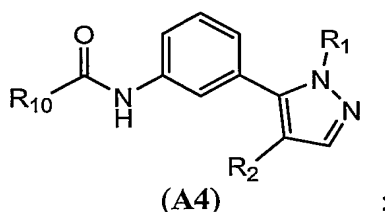
cyclizing a compound of Formula (A2) with a compound of Formula (B2):



the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of
Formula (A3):

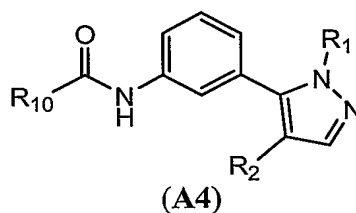


halogenating a compound of Formula (A3) with a halogenating reagent in a halogenating
solvent to yield a compound of Formula (A4);

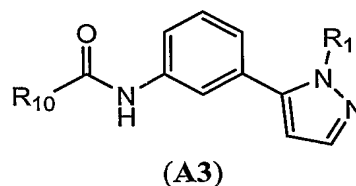


and hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5); wherein R₁ is C₁₋₂ alkyl; R₁₀ is C₁₋₆ alkyl; R₁₁ is C₁₋₃ alkyl; and R₁₂ is C₁₋₆ alkyl or alkylaryl; or both R₁₂ groups together form a 5 or 6 membered heterocyclic ring. In some embodiments the compound of Formula (B1) is *N,N*-dimethylformamide dimethyl acetal. In some embodiments the condensing solvent is ethanol and the condensing step is conducted at a temperature of about 25°C to about 95°C. In some embodiments the condensing step is conducted at a temperature of about 70°C to about 80°C. In some embodiments the process further comprises a cyclizing acid in the cyclizing step and the cyclizing acid is hydrochloric acid. In some embodiments the compound of Formula (B2) is methyl hydrazine and the cyclizing solvent is methanol. In some embodiments the halogenating reagent is *N*-bromosuccinimide or *N*-chlorosuccinimide, the halogenating solvent is *N,N*-dimethylformamide, and the halogenating step is conducted between about 20°C to about 60°C. In some embodiments the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted between about 60°C to about 80°C.

Some embodiments of the invention include a process for making a compound of Formula (A4):

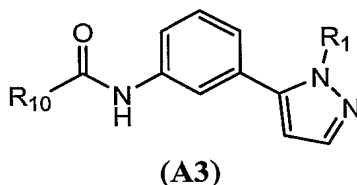


the process comprising the steps of halogenating a compound of Formula (A3):

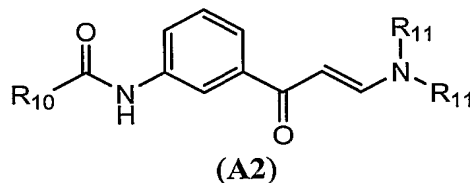


with a halogenating reagent in a halogenating solvent to yield the compound of Formula (A4); wherein R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; and R₁₀ is C₁₋₆ alkyl. In some embodiments the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide. In some
 5 embodiments the halogenating reagent is N-bromosuccinimide and the halogenating solvent is N,N-dimethylformamide. In some embodiments the halogenating step is conducted between about 20°C to about 60°C.

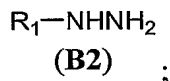
Some embodiments of the invention include a process for making a compound of Formula (A3):



10 the process comprising the steps of cyclizing a compound of Formula (A2):

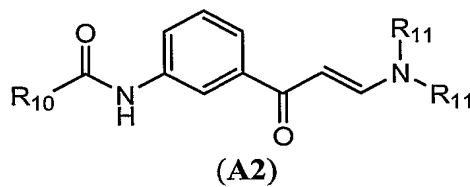


with a compound of Formula (B2):

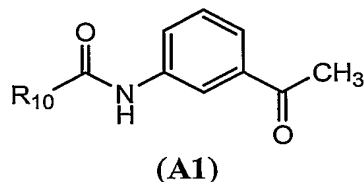


15 the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (A3); wherein R₁ is C₁₋₂ alkyl; R₁₀ is C₁₋₆ alkyl; and R₁₁ is C₁₋₃ alkyl. In some embodiments the process further comprises a cyclizing acid in the cyclizing step. In some embodiments the cyclizing acid is hydrochloric acid. In some embodiments the compound of Formula (B2) is methyl hydrazine. In some embodiments the cyclizing solvent is methanol.

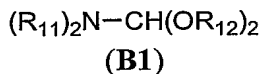
20 Some embodiments of the invention include a process for making a compound of Formula (A2):



the process comprising the steps of condensing a compound of Formula (A1):

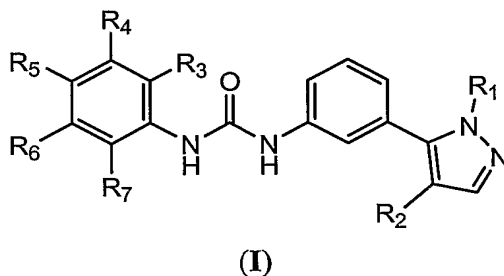


with a compound of Formula (B1):

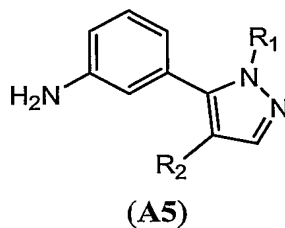


- 5 the condensing step is optionally conducted in an condensing solvent to yield a compound of Formula (A2); wherein R_{10} is C_{1-6} alkyl; R_{11} is C_{1-3} alkyl; and R_{12} is C_{1-6} alkyl or alkylaryl; or both R_{12} groups together form a 5 or 6 membered heterocyclic ring. In some embodiments the compound of Formula (B1) is *N,N*-dimethylformamide dimethyl acetal. In some embodiments the condensing solvent is ethanol and the
- 10 condensing step is conducted at a temperature of about 25°C to about 95°C.

Some embodiments of the invention relate to a process for making a compound of Formula (I):

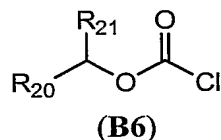


the process comprising a step of reacting a compound of Formula (A5):

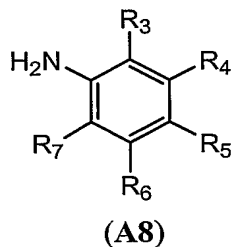


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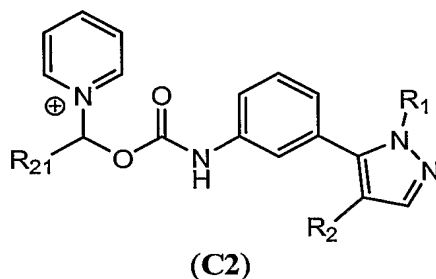
with a substituted alkyl chloroformate of Formula (B6):



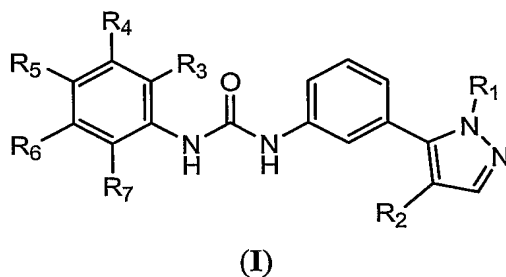
and an organic base in a non-reactive solvent to give an intermediate; the intermediate is subsequently involved in a coupling with a compound of Formula (A8):



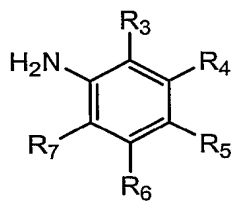
to yield a compound of Formula (I); wherein R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; R₃, R₄, R₅, R₆ and R₇ are each independently selected from H, halogen, or haloalkyl; provided that at least one R₃, R₄, R₅, R₆ and R₇ is not H; R₂₀ is a Cl, Br, I, mesylate or tosylate; and R₂₁ is a C₁-C₈ alkyl;. In some embodiments the organic base is pyridine. In some embodiments the non-reactive solvent is methylene chloride. In some embodiments the intermediate has the Formula (C2):



In an alternative manner, some embodiments of the invention relate to a process for making a compound of Formula (I):

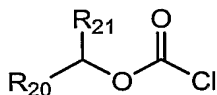


the process comprising a step of reacting a compound of Formula (A8):



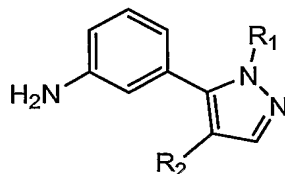
(A8)

with a substituted alkyl chloroformate of Formula (B6):



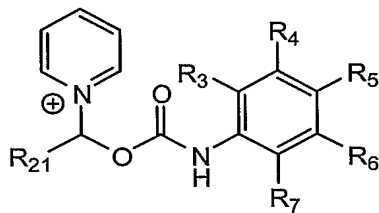
(B6)

and an organic base in a non-reactive solvent to give an intermediate. The intermediate is subsequently coupled with a compound of Formula (A5):



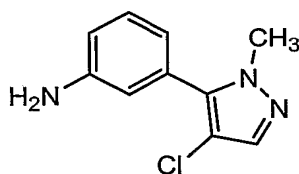
(A5)

wherein R₁ and R₂ have the same meaning as described above; to yield the compound of Formula (I); wherein R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; R₃, R₄, R₅, R₆ and R₇ are each independently selected from H, halogen, or haloalkyl; provided that at least one R₃, R₄, R₅, R₆ and R₇ is not H; R₂₀ is a Cl, Br, I, mesylate or tosylate; and R₂₁ is a C₁-C₈ alkyl. In some embodiments the process the organic base is pyridine. In some embodiments the non-reactive solvent is methylene chloride. In some embodiments of the process the intermediate is Formula (C4):

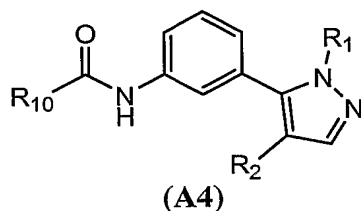


(C4)

Some embodiments of the invention include a compound of the Formula:

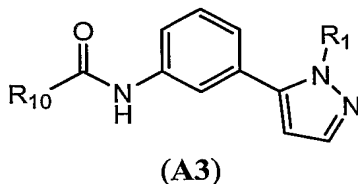


Some embodiments of the invention include a compound of Formula (A4):



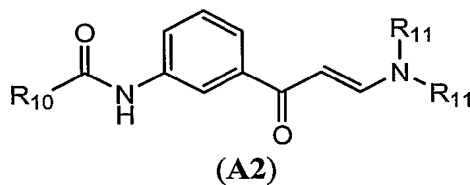
wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{10} is C_{1-6} alkyl. In some
 5 embodiments R_1 and R_{10} are both CH_3 , and R_2 is Br.

Some embodiments of the invention include a compound of Formula (A3):



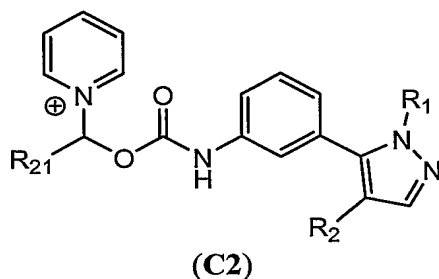
wherein R_1 is C_{1-2} alkyl; and R_{10} is C_{1-6} alkyl. In some embodiments R_1 and R_{10}
 are both CH_3 .

Some embodiments of the invention include a compound of Formula (A2):



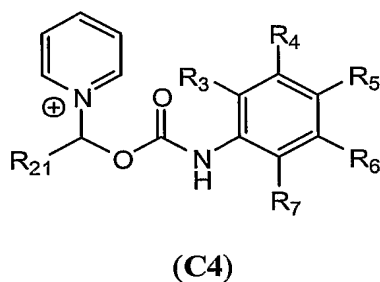
wherein R_{10} is C_{1-6} alkyl; and R_{11} is C_{1-3} alkyl. In some embodiments R_{10} and R_{11}
 are both CH_3 .

Some embodiments of the invention include a compound of Formula (C2):



wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{21} is C_1 - C_8 alkyl. In some embodiments a compound of Formula (C2) are when R_1 is CH_3 ; R_2 is Br; and R_{21} is CH_3 .

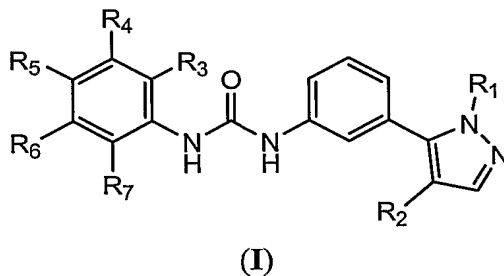
Some embodiments of the invention include a compound of Formula (C4):



wherein R_3 , R_4 , R_5 , R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; and R_{21} is C_1 - C_8 alkyl. In some embodiments compounds of Formula (C3) are when R_3 , R_4 , R_5 , R_6 and R_7 are each independently selected from H, F or Cl; and R_{21} is CH_3 .

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the invention encompasses a process for making compounds of Formula (I) useful in the prophylaxis or treatment of $5HT_{2A}$ mediated disorders:



wherein:

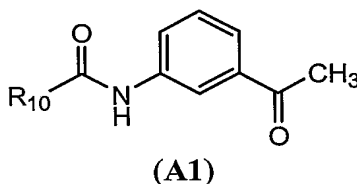
R_1 is C_{1-2} alkyl;

R_2 is Cl or Br;

R_3 , R_4 , R_5 , R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; comprising the steps of:

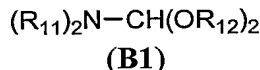
Step (i)

Condensing a compound of Formula (A1):



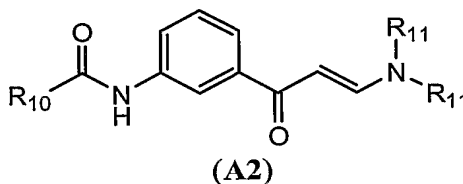
wherein R_{10} is C_{1-6} alkyl;

with a compound of Formula (B1):



wherein R_{11} is C_{1-3} alkyl; and R_{12} is C_{1-6} alkyl or alkylaryl; or both R_{12} groups together form a 5 or 6 membered heterocyclic ring;

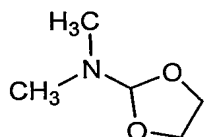
the condensing step is optionally conducted in a condensing solvent to yield a compound Formula (A2). A compound of Formula (A2) is also referred to as an enaminone and is of the formula:



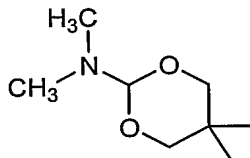
In reference to Formula (A1), the acyl group, formed by the R_{10} group together with the carbonyl, serves as an amino protecting group in step (i), the resulting group is more commonly referred to an amide group. A variety of groups for R_{10} may be utilized provided that the resulting acyl group bearing the R_{10} group can be removed as described in step (iv). R_{10} may be selected from, but not limited to, the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, pentyl, neopentyl and hexyl. Preferably R_{10} is methyl.

A variety of *N,N*-dialkylformamide acetals of the Formula (B1) may be used in step (i). For example, R_{11} may be selected from, but not limited to, the group consisting of methyl, ethyl, propyl and iso-propyl. Preferably R_{11} is methyl. When R_{12} is alkyl, then R_{12} may be selected from, but not limited to, the group consisting of methyl, ethyl,

propyl, iso-propyl, n-butyl, *tert*-butyl and neopentyl. Preferably R₁₂ is methyl. Examples of *N,N*-dialkylformamide acetals of Formula (B1) when R₁₂ is alkyl include for example, *N,N*-dimethylformamide dimethyl acetal, *N,N*-dimethylformamide diethyl acetal, *N,N*-dimethylformamide dipropyl acetal, *N,N*-dimethylformamide diisopropyl acetal, *N,N*-dimethylformamide dibutyl acetal, *N,N*-dimethylformamide di-*tert*-butyl acetal and *N,N*-dimethylformamide dineopentyl acetal. When R₁₂ is cycloalkyl, then R₁₂ may be selected from, but not limited to, the group consisting of cyclopentyl or cyclohexyl. One example of an *N,N*-dialkylformamide acetal of Formula (B1) when R₁₂ is cycloalkyl includes *N,N*-dimethylformamide dicyclohexyl acetal. When R₁₂ is C₁₋₂ alkylaryl, then R₁₂ is selected from, but not limited to, the group consisting of benzyl, 1-phenylethyl and 2-phenylethyl. One example of an *N,N*-dialkylformamide acetal of the Formula (B1) when R₁₂ is C₁₋₂ alkylaryl includes, *N,N*-dimethylformamide dibenzyl acetal. When both R₁₂ groups together form a 5 or 6 membered heterocyclic ring, then the *N,N*-dialkylformamide acetal of Formula (B1) may be selected from, but not limited to, the group consisting of *N,N*-dimethylformamide ethylene acetal and *N,N*,5,5-tetramethyl-1,3-dioxan-2-amine and are represented by the following structure:

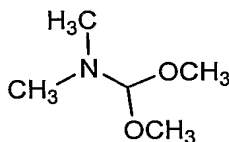


N,N-dimethylformamide
ethylene acetal



N,N,5,5-tetramethyl-
1,3-dioxan-2-amine.

Preferably, R₁₁ and R₁₂ are both methyl and the compound is represented by the following structure:



N,N-dimethylformamide
dimethyl acetal.

The condensing solvent may optionally be present or absent. In the instance that the condensing solvent is absent then the *N,N*-dialkylformamide dialkylacetal of Formula (B1) serves both as a reactant in condensation step (i) and as the solvent. When

a condensing solvent is present, the solvent is selected from, but not limited to, the group consisting of methanol, ethanol, butanol, pentanol, 1-propanol and 2-propanol.

Preferably the condensing solvent is present and preferably the solvent is ethanol.

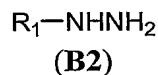
The condensing step is conducted at a temperature between about 25°C to about 95°C. Preferably the condensing step is conducted at a temperature between about 50°C to about 85°C and most preferably between about 70°C to about 80°C.

Generally, the molar ratio of an acetophenone of Formula (A1) to an *N,N*-dialkylformamide dialkyl acetal of Formula (B1) is such that the *N,N*-dialkylformamide dialkyl acetal is used in excess. Typically, when the condensing solvent is absent, then the molar ratio of the acetophenone to the *N,N*-dialkylformamide dialkyl acetal is in a ratio of 1 to at least about 1. Stated differently, when the solvent is absent, the *N,N*-dialkylformamide dialkyl acetal is present in at least about 1 molar equivalent compared to the acetophenone. Any amount of *N,N*-dialkylformamide dialkyl acetal in excess of this about 1 molar equivalent may serve the role of a solvent or some other function, such as, to increase the rate of the reaction, improve mechanical manipulation (i.e., stirring, mixing) and the like. When the condensing solvent is present, the molar ratio of an acetophenone of Formula (A1) to a *N,N*-dialkylformamide dialkyl acetal of Formula (B1) is typically about 1:1 to about 1:3, and preferably the ratio is between about 1:1.1 to about 1:2. The presence of the *N,N*-dialkylformamide dialkyl acetal outside these ranges in excess may be determined by methods known in the art.

Step (ii)

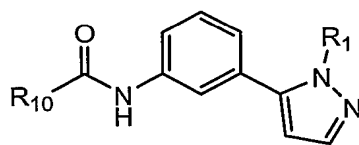
Cyclizing a compound of Formula (A2) with a compound of Formula (B2).

Compounds of Formula (B2) are also referred to as an alkylhydrazine and are of the formula:



wherein R₁ is C₁₋₂ alkyl;

the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (A3);



(A3)

Preferably, the alkylhydrazine is methyl hydrazine and R_1 is methyl. The cyclizing solvent may optionally be present or absent. In the instance that the cyclizing solvent is absent then the alkylhydrazine of Formula (B2) serves both as a reactant in the cyclization step (ii) and as the solvent. When a cyclizing solvent is present, the solvent is selected from, but not limited to, the group consisting of methanol, ethanol, butanol, pentanol, 1-propanol and 2-propanol. Preferably the cyclizing solvent is present and preferably the solvent is methanol.

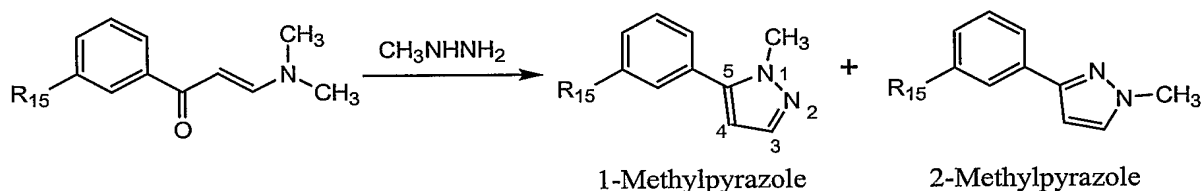
In some embodiments, the cyclizing step (ii) further comprises the addition of a cyclizing acid, selected from, but not limited to, the group consisting of hydrochloric acid, hydrobromic acid, acetic acid and trifluoroacetic acid; the cyclizing acid is preferably hydrochloric acid. In some embodiments the molar ratio of the alkylhydrazine and cyclizing acid is typically between the range of about 1:0.1 to about 1:20; in another embodiment the molar ratio of the alkylhydrazine and cyclizing acid is between about 1:05 to about 1:12 and preferably the range is between about 1:1 to about 1:8.

Generally, the molar ratio of the enaminone of Formula (A2) to alkylhydrazine of Formula (B2) is such that the alkylhydrazine is present in excess. Typically, when the cyclization solvent is absent, then the molar ratio of the enaminone of Formula (A2) to the compound of Formula (B2) is in a ratio of 1 to at least 1. Stated differently, when the solvent is absent, the alkylhydrazine is present in at least about 1 molar equivalent compared to the enaminone of Formula (A2). Any amount of alkylhydrazine in excess of this about 1 molar equivalent serves as the role of a solvent or some other function, such as, to increase the rate of the reaction, improve mechanical manipulation (i.e., stirring, mixing) and the like. When the cyclization solvent is present, in general the molar ratio of the enaminone to alkylhydrazine is between about 1:1 to about 1:3; another range is typically between about 1:1 to about 1:1.5; and preferably the range is between about 1:1 to about 1:1.2. The cyclizing step is conducted at a temperature between about -25°C to about 60°C , preferably the cyclizing step is conducted at a temperature between about

−10°C to about 25°C.

Some embodiments of the invention show a high degree of regioselectivity in the cyclization; **TABLE 1** illustrates the ratio of 2-methylpyrazole to 1-methylpyrazole.

TABLE 1



R ₁₅	Temperature (°C)	RATIO	
		1-Methylpyrazole	2-Methylpyrazole
NO ₂ [*]	0 to RT	84	16
CH ₃ CONH [*]	0 to RT	86	14
CH ₃ CONH ^{**}	0 to RT	91	9

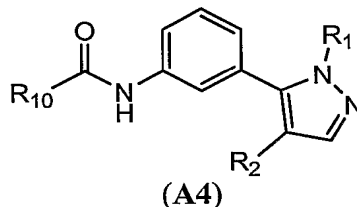
^{*} 3.2 eq. of HCl and 1.16 eq of methylhydrazine were used in the reaction.

^{**} 6.0 eq of HCl and 1.12 eq of methylhydrazine were used in the reaction.

See Examples for additional information, *infra*.

Step (iii)

Halogenating a compound of Formula (A3) with a halogenating reagent in a halogenating solvent to yield a compound of Formula (A4);



In one embodiment when R₂ is Br, the halogenating reagent may be selected from the available reagents known in the art, such as, for example, N-bromosuccinimide (i.e., NBS), 1,3-dibromo-5,5-dimethylhydantoin, pyridinium tribromide (pyrHBr₃) and the like; preferably, N-bromosuccinimide is the halogenating reagent for when R₂ is Br. This step is superior to the use of bromine (i.e., Br₂) in the bromination step. For example, the use of bromine in CH₂Cl₂ required large stoichiometric excess of bromine and excessive reaction times. Even under these conditions the reaction gave selectivity difficulties as observed by the presence of significant amounts of unconverted starting material and

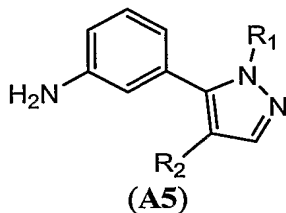
dibrominated by products. Furthermore, the use of bromine CH_2Cl_2 gave heterogeneous reaction mixtures and reaction monitoring difficulties.

Based in part on the discovery of the brominating reagent, the halogenating reagent is preferably N-chlorosuccinimide (i.e., NCS) for when R_2 is Cl.

Generally, the molar ratio of a compound of Formula (A3) to halogenating reagent is typically in the range varying between a ratio of about 1:0.9 to about 1:1.1; preferably the range is between about 1:0.95 to about 1:1.05. The use of excess halogenating reagent may lead to the incorporation of multiple bromines into the product. The halogenating solvent is a suitable polar solvent such as *N,N*-dimethylformamide (i.e., DMF), methylsulfoxide, acetonitrile, ethyl acetate, methylene chloride and the like; preferably the solvent is DMF. One beneficial feature in the use of a water soluble halogenating solvent such as DMF, is the particular ease in separating the resulting product of step (iii) from the solvent. To illustrate this point, where DMF and NBS were used in the halogenating step (iii), the resulting product was isolated by the addition of water. After the addition, the product was allowed to crystallize from the halogenating mixture to yield the desired compound in high yield and purity, 92% and 99.2% respectively. A similar result was seen in the example of DMF and NCS, *infra*.

Typically the halogenating step is conducted at a temperature between about 10°C to about 80°C , preferably the halogenating step is conducted at a temperature between about 20°C to about 60°C .

(iv) Hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5):



Suitable bases for this step include, for example, alkali metal hydroxides such as lithium hydroxide, sodium hydroxide or potassium hydroxide. Preferably, the alkali metal hydroxide is sodium hydroxide.

Generally, the molar ratio of a compound of Formula (A4) to alkali metal hydroxide is typically in the range varying between a ratio of about 1:1 to about 1:10;

another range is typically between about 1:3 to about 1:8; preferably the range is between about 1:4 to about 1:6.

The aqueous hydrolyzing solvent is a mixture of water with a suitable polar solvent selected from the group consisting of tetrahydrofuran (THF), methanol, ethanol, 1-propanol, 2-propanol, butanol and pentanol; included are mixtures thereof. Preferably the polar solvent is ethanol. The amount of water present is typically determined by the amount necessary to dissolve the corresponding alkali metal hydroxide. The hydrolyzing step is conducted at a temperature between about 20°C to about 100°C. Preferably the condensing step is conducted at a temperature between about 50°C to about 85°C and most preferably between about 60°C to about 80°C.

Surprisingly, acid hydrolysis using, for example, 2 equivalents of HCl in boiling ethanol, resulted in both the desired deacetylation leading to a compound of Formula (A5) and also to at least one undesirable side-reaction. One presumed side-reaction under acidic conditions is the disproportionation of certain compounds of Formula (A4). Several products resulting from disproportionation were identified as aniline derivatives containing either no bromine atoms or 2 bromine atoms. These compounds not only contributed to the impurity profile for this step but also removed material that would otherwise be converted to product. Representative data comparing acidic and alkaline are shown in Examples, *infra*.

This problem was overcome by utilizing alkaline conditions as described herein. One representative example using alkaline conditions is in the deacetylation of 5-(3'-acetaminophenyl)-4-bromo-1-methyl-1*H*-pyrazole to 5-(3'-aminophenyl)-4-bromo-1-methyl-1*H*-pyrazole giving 95.9 % overall yield with no detectable side-products.

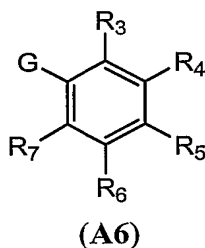
Urea Forming Steps

The following steps are alternatives to forming the urea moiety in compounds of the invention. In general, Step (v) may use a commercially available aryl isocyanate or one that can be prepared by known methods and coupled with the aniline of Formula (A5) to yield a compound of Formula (I). An analogous two-part step is described in Steps (vi) and (vii) in which the isocyanate is prepared (i.e., Step (vi)) from the aniline of Formula (A5) and subsequently coupled (i.e., Step (vii)) with the aniline of Formula

(A8). Step (viii) is yet another urea forming step. In this step, an aniline of Formula (A5) may be reacted with a substituted alkyl chloroformate in the presence of an organic base to give in intermediate that is subsequently coupled with an aniline of Formula (A8). This step may be modified, as illustrated in Step (ix) to give yet another urea forming step, namely, aniline of Formula (A8) may be reacted with a substituted alkyl chloroformate to give an intermediate that is reacted with an aniline of Formula (A5). The following sections provide additional details of these steps.

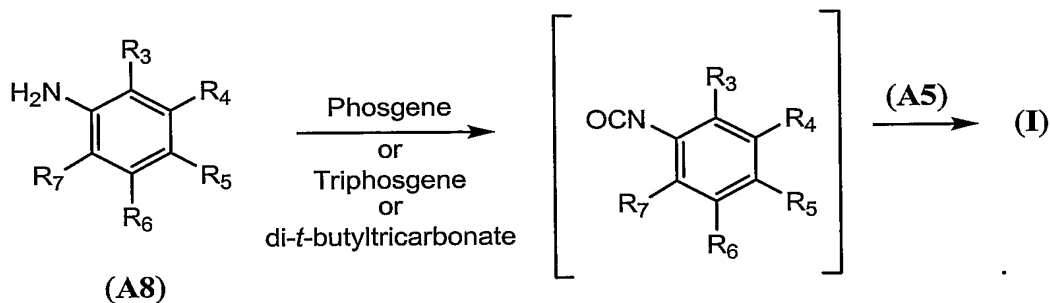
1. Step (v)

Coupling a compound of Formula (A5) with a compound of Formula (A6):



wherein R₃, R₄, R₅, R₆ and R₇ have the same definitions as described above; and G is an isocyanate or isocyanate equivalent group; the coupling step being conducted in a coupling solvent to give a compound of Formula (I).

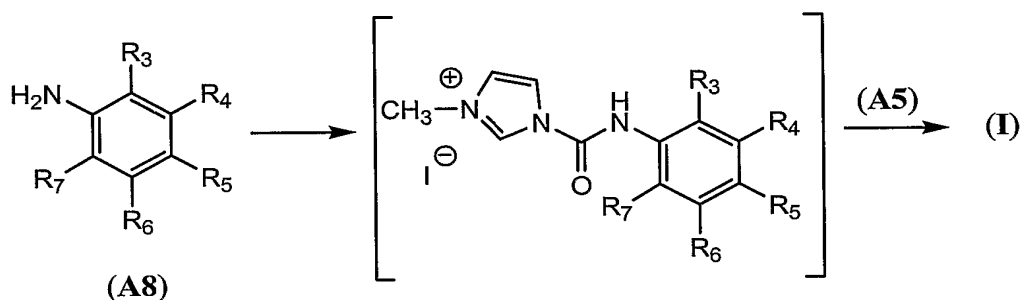
A suitable G group in step (v) is an isocyanate (-N=C=O) or isocyanate equivalent. Isocyanates and isocyanate equivalents are well known in the art; many isocyanates are commercially available. For those isocyanates that are not commercially available, they may be readily prepared utilizing the corresponding anilines, for example, the use of phosgene (i.e., Cl₂C=O) or triphosgene [i.e., bis-trichloromethyl carbonate, Cl₃COC(O)OCCl₃] to generate the isocyanate *in situ* or isolated for subsequent use. Another procedure using di-*t*-butyltricarboxylate generate isocyanates from anilines in a similar manner as described above has been reported by Peerlings et al. in *Tetrahedron Lett.* **1999**, *40*, 1021-1024. These procedures and others known in the art may give rise to useful isocyanates as illustrated in Scheme 1 below:



Scheme 1

Alternatively, isocyanate equivalents may also be used and prepared from the corresponding aniline by the sequential action of carbonyl diimidazole and methyl iodide in THF and acetonitrile respectively as described by Batey et al. in *Tetrahedron Lett.*

1998, 39, 6267-6270. This procedure may give rise to useful isocyanate equivalents as illustrated in the reaction scheme below:



Scheme 2

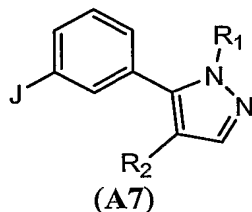
Generally, the molar ratio of a compound of Formula (A5) to a compound of Formula (A6) is typically in the range of varying between about 1:1 to about 1:1.5; preferably about 1:1 to about 1:1.2. The coupling solvent is a suitable non-reactive solvent such as *N,N*-dimethylformamide (i.e., DMF), methylsulfoxide, acetonitrile, ethyl acetate, methylene chloride and the like; preferably the solvent is methylene chloride. The coupling step (v) is typically conducted at a temperature between about 0°C to about 60°C; preferably the temperature is between about 10°C to about 45°C.

2. Step (vi)

An alternative process to step (v) is described below. This alternative embodiment comprises a compound of Formula (A5) that may be converted into a compound bearing an isocyanate or isocyanate equivalent in a manner described above.

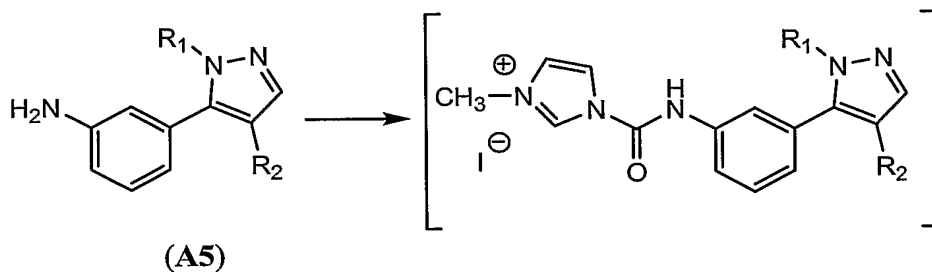
This alternative embodiment comprises two steps identified as steps (vi) and (vii); these steps are specifically described, *infra*.

Reacting a compound of Formula (A5) with an isocyanate generating reagent in an isocyanate generating solvent to yield a compound of Formula (A7):



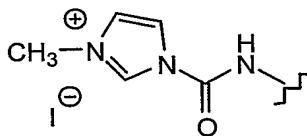
wherein J is an isocyanate or isocyanate equivalent;

The isocyanate generating reagent may be selected from the available reagents known in the art including those described herein, such as, phosgene, triphosgene or di-*t*-butyltricarboxylate, wherein the resulting product is of Formula (A7) and J is -N=C=O. An isocyanate generating reagent is also defined as forming a chemical species that reacts in a manner comparable to an isocyanate, such as the chemical species shown in brackets in Scheme 3 below:



Scheme 3

In this example J is considered as an isocyanate equivalent and is represented by the Formula shown below:



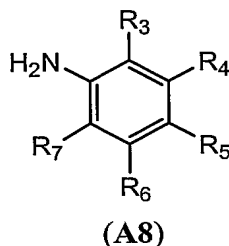
Generally, the molar ratio of a compound of Formula (A5) to an isocyanate generating reagent is typically in the range varying between about 1:1 to about 1:2; preferably about 1:1 to about 1:1.2. The isocyanate generating solvent is a suitable non-reactive solvent such as *N,N*-dimethylformamide (i.e., DMF), methylsulfoxide, acetonitrile, tetrahydrofuran (i.e., THF), ethyl acetate, methylene chloride, toluene and

the like; preferably the solvent is methylene chloride, acetonitrile, THF or toluene; and most preferably, the solvent is substantially free of water. The coupling step (vi) is typically conducted at a temperature between about -10°C to about 60°C; preferably the temperature is between about 10°C to about 50°C.

It is generally understood in the art that although the isocyanate or isocyanate equivalent may be isolated it may not always be necessary to do so and that this fact would be recognized by the artisan. Therefore, in certain instances the isocyanate or isocyanate equivalent may be generated *in situ* and reacted directly with the appropriate aniline without isolation.

Step (vii)

Coupling the compound of Formula (A7) with a compound of Formula (A8):



wherein R₃, R₄, R₅, R₆ and R₇ have the same meaning as described herein, *supra*; the coupling step being conducted in a coupling solvent to give a compound of Formula (I).

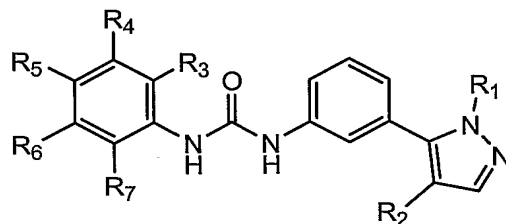
Generally, the molar ratio of a compound of Formula (A7) to a compound of Formula (A8) is typically in the range varying between about 1:1 to about 1:1.5; preferably about 1:1 to about 1:1.2. The coupling solvent is a suitable non-reactive solvent such as *N,N*-dimethylformamide (i.e., DMF), methylsulfoxide, acetonitrile, ethyl acetate, methylene chloride and the like; preferably the solvent is methylene chloride. The coupling step (vii) is typically conducted at a temperature between about 0°C to about 60°C; preferably the temperature is between about 10°C to about 50°C.

3. Step (viii)

Step (viii) is yet another urea forming step. This is an alternative process step to that of step (v), *supra*, to yield compounds of the inventions. This alternative embodiment comprises a compound of Formula (A5) that may be converted into a

compound bearing an isocyanate or isocyanate equivalent in a analogous manner as described above. This alternative embodiment comprises the making of an intermediate that may be isolated or directly coupled with a compound Formula (A6); this particular step is identified as step (viii) and is specifically described *infra*.

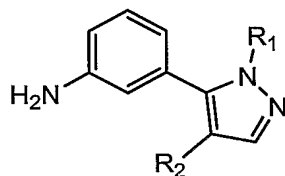
Some embodiments of the invention relate to a process for making a compound of Formula (I):



(I)

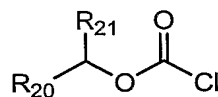
wherein R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; and R₃, R₄, R₅, R₆ and R₇ are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H. This process comprises the step of:

reacting a compound of Formula (A5):



(A5)

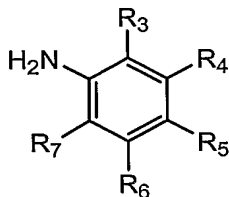
wherein R₁ and R₂ have the same meaning as described above, with a substituted alkyl chloroformate of Formula (B6):



(B6)

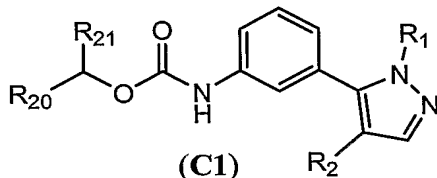
wherein R₂₀ is a leaving group, such as, Cl, Br, I, mesylate, tosylate, and the like; and R₂₁ is a C₁-C₈ alkyl; such as, methyl, ethyl, propyl, butyl, pentyl, isopropyl, neopentyl, hexyl, octyl and the like; in the presence of an organic base; such as, pyridine, dimethylaminopyridine, piperidine, morpholine and the like. In some embodiments the organic base is pyridine. This step is conducted in a non-reactive solvent to give an intermediate. The non-reactive solvent is a suitable polar solvent, such as *N,N*-

dimethylformamide (i.e., DMF), methylsulfoxide, acetonitrile, ethyl acetate, tetrahydrofuran (i.e., THF), methylene chloride and the like; preferably the solvent is methylene chloride. The intermediate formed, may be isolated or subsequently used in a coupling reaction with a compound of Formula (A8):



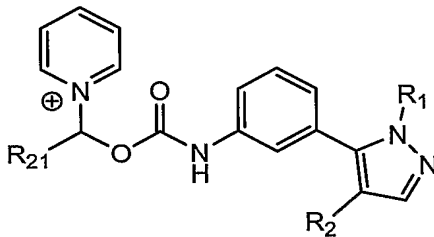
(A8)

wherein R₃-R₇ have the same meaning as described above, to yield a compound of Formula (I). The intermediate may have the structure of Formula (C1) shown below:



(C1)

where R₁, R₂ and R₂₁ have the same definition as described *supra*. Intermediate (C1) may result from the addition of a compound of Formula (A5) to the substituted alkyl chloroformate. Another intermediate may have the structure of Formula (C2):



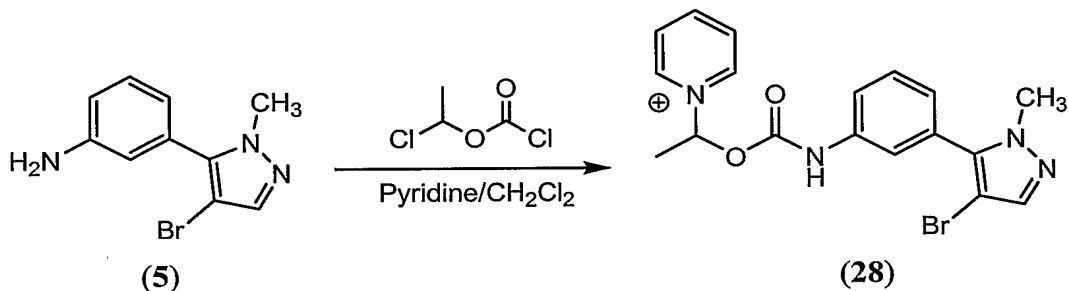
(C2)

where R₁, R₂ and R₂₁ have the same definition as described *supra*. Intermediate (C2) may arise from displacement of the R₂₀ leaving group by the organic base (i.e., pyridine) and subsequent addition of a compound of Formula (A5); or from the displacement of the R₂₀ by the organic base of the intermediate (C1). Optionally, an additional organic base, such as one described *supra* for this step, may be used in reacting the intermediate with an aniline of Formula (A5).

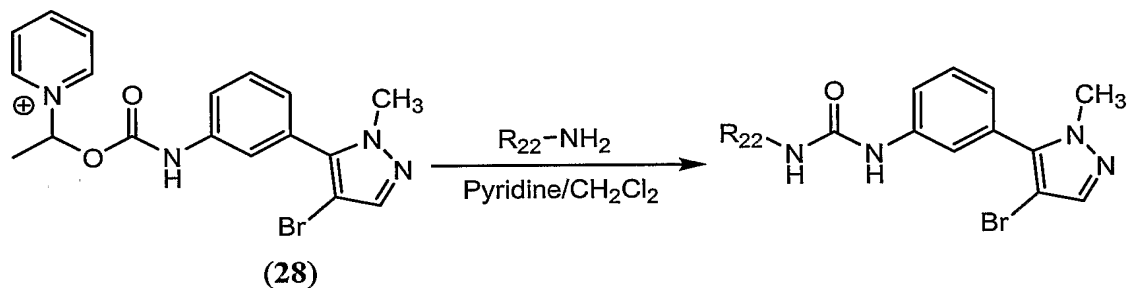
Generally, the molar ratio of a compound of Formula (A5) to a substituted alkyl chloroformate of Formula (B6) is typically in the range varying between about 1:1 to

about 1:2; preferably about 1:1 to about 1:1.5. Step (vii) may be conducted at a temperature between about 0°C to about 60°C; preferably the temperature is between about 10°C to about 45°C.

By way of an example, when 5-(3-aminophenyl)-4-bromo-1-methylpyrazole (5) was treated with a substituted alkyl chloroformate, such as, 1-chloroethyl chloroformate a pyridinium salt (28) was isolated as shown below:

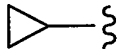
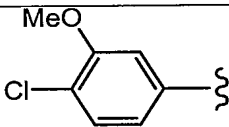


The resulting pyridinium salt (28), when treated with a variety of amines, such as, isopropyl amine, 2-aminothiazole, cyclopropyl amine, 4-chloro-3-methoxyaniline, and the like, gave the coupled products, as illustrated in the reaction scheme below:



Representative examples are shown in the table below:

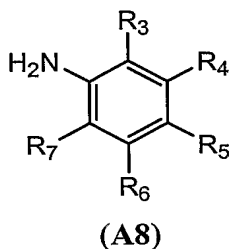
Compound No.	R
29	
30	

31	
32	

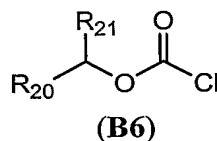
4. Step (ix)

In an alternative but analogous manner to step (viii), step (ix) may be conducted using the aniline of Formula (A8) and treating it with a substituted alkyl chloroformate of Formula (B6) to generate an intermediate, which in turn may be coupled with a compound of Formula (A5) to yield a compound of Formula (I). Additional details of Step (ix) are specifically described *infra*.

This process comprises the step of reacting a compound of Formula (A8):

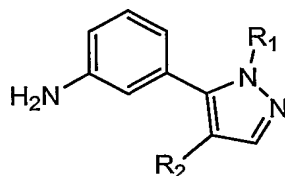


wherein R_3 , R_4 , R_5 , R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; with a substituted alkyl chloroformate of Formula (B6):



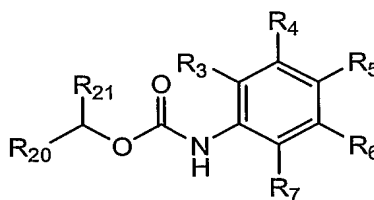
wherein R_{20} is a Cl, Br, I, mesylate or tosylate, and the like; and R_{21} is a C_1 - C_8 alkyl, such as those examples described *supra*. This reaction is conducted in the presence of an organic base, such as, pyridine, dimethylaminopyridine, piperidine, morpholine and the like; in a non-reactive solvent to give an intermediate. In some embodiments, the organic base is pyridine. The non-reactive solvent can be one of the solvents described in step

(viii). Preferably the solvent is methylene chloride. The intermediate is subsequently involved in a coupling with a compound of Formula (A5):



(A5)

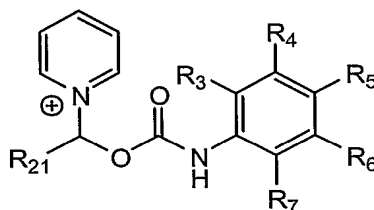
wherein R₁ is C₁₋₂ alkyl; and R₂ is Cl or Br; to yield the compound of Formula (I). The intermediate may be represented by the structure shown below:



(C3)

wherein R₃, R₄, R₅, R₆, R₇, R₂₀ and R₂₁ have the same meaning as described, *supra*. Intermediate (C3) may result from the addition of a compound of Formula (A8) to the substituted alkyl chloroformate.

Another intermediate may have the structure of Formula (C4):



(C4)

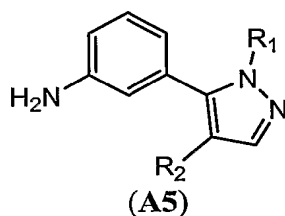
;

wherein R₃, R₄, R₅, R₆, R₇, R₂₀ and R₂₁ also have the same meaning as described, *supra*. Intermediate (C4) may arise from displacement of the R₂₀ leaving group by the organic base (i.e., pyridine) and subsequent addition of a compound of Formula (A8); or from the displacement of the R₂₀ by the organic base of intermediate (C3).

Optionally, an additional organic base, such as one described *supra* for this step, may be used in reacting the intermediate with an aniline of Formula (A5).

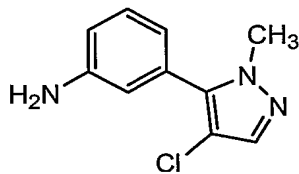
Generally, the molar ratio of a compound of Formula (A8) to a substituted alkyl chloroformate Formula (B6) is typically in the range varying between about 1:1 to about 1:2; preferably about 1:1 to about 1:1.5. This step may be conducted at a temperature between about 0°C to about 60°C; preferably the temperature is between about 10°C to about 45°C.

In a second aspect, the invention encompasses a process for making compounds that are useful as intermediates in the process for making compounds of Formula (I). One embodiment is a process for making a compound of Formula (A5):

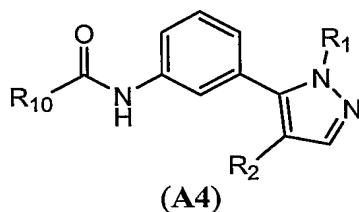


wherein R₁ is C₁₋₂ alkyl; and R₂ is Cl or Br. The steps for the making compounds of Formula (A5) are described, *supra*.

In a third aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (I) wherein the intermediate is of the following structure:

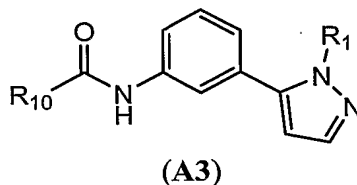


In a fourth aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (I) wherein the intermediate is of Formula (A4):



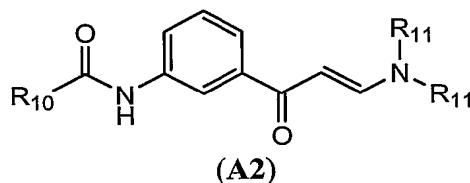
wherein R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; and R₁₀ is C₁₋₆ alkyl, preferably R₁ and R₁₀ are both CH₃, and R₂ is Br.

In a fifth aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (I) wherein the intermediate is of Formula (A3):



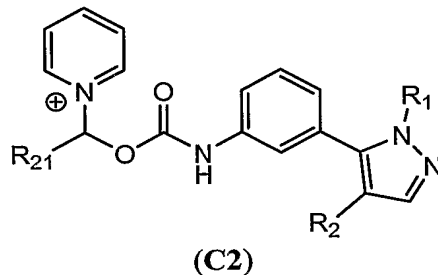
wherein R₁ is C₁₋₂ alkyl; and R₁₀ is C₁₋₆ alkyl, preferably R₁ and R₁₀ are both CH₃.

5 In a sixth aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (I) wherein the intermediate is of Formula (A2):



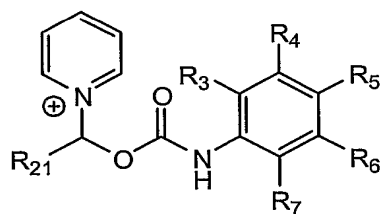
wherein R₁₀ is C₁₋₆ alkyl; and R₁₁ is C₁₋₃ alkyl, preferably R₁₀ and R₁₁ are both CH₃.

10 In a seventh aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (I) wherein the intermediate is of Formula (C2):



wherein R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; and R₂₁ is C₁₋₈ alkyl. Preferably, R₁ is CH₃; R₂ is Br; and R₂₁ is CH₃.

15 In an eighth aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (I) wherein the intermediate is of Formula (C4):



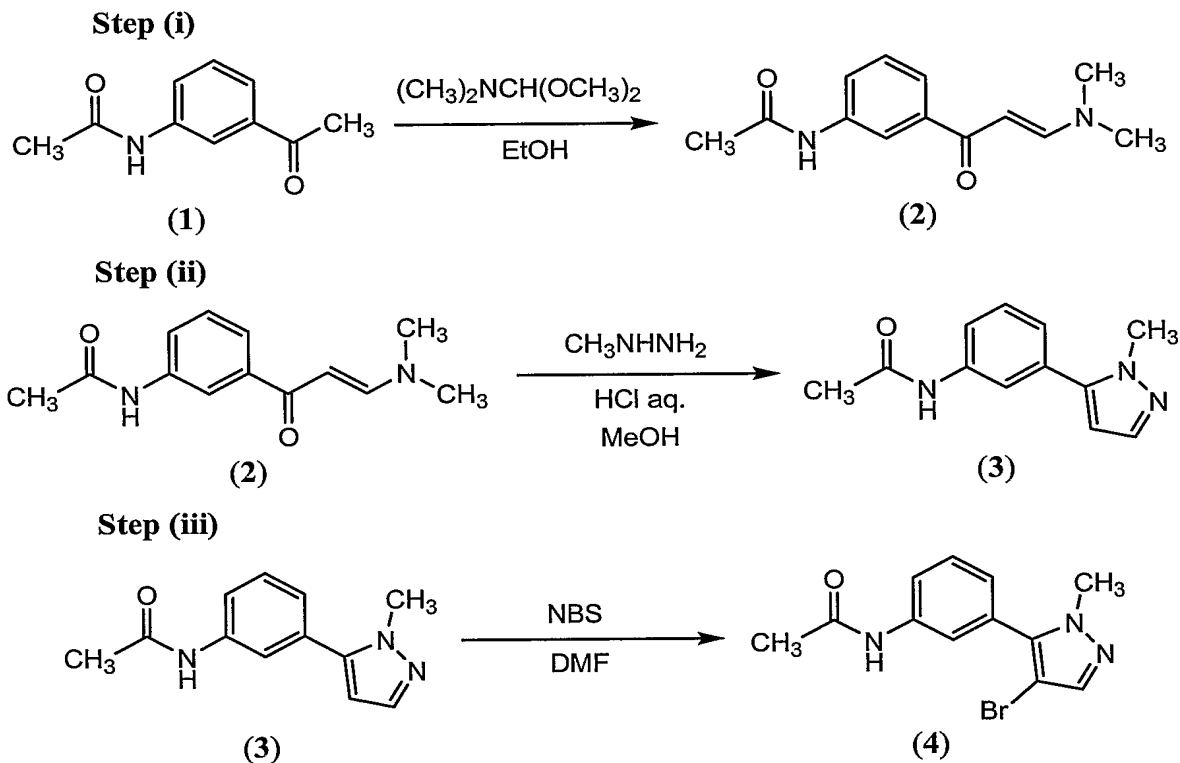
(C4)

;

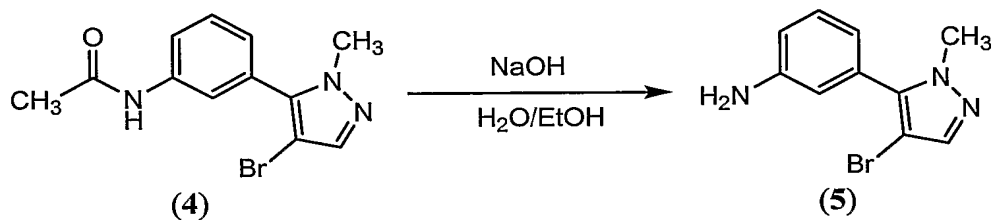
wherein R_3 , R_4 , R_5 , R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; and R_{21} is C_1 - C_8 alkyl. Preferably, R_3 , R_4 , R_5 , R_6 and R_7 are each independently selected from H, F or Cl; provided that at least one is not H; and R_{21} is CH_3 .

The invention is further illustrated in the following steps wherein preferred reactants are shown to more clearly demonstrate the process disclosed. In Scheme 4, R_1 , R_{10} and R_{11} are each methyl; R_2 is bromo, R_3 , R_4 , R_6 , R_7 are each hydrogen; and R_5 is chloro.

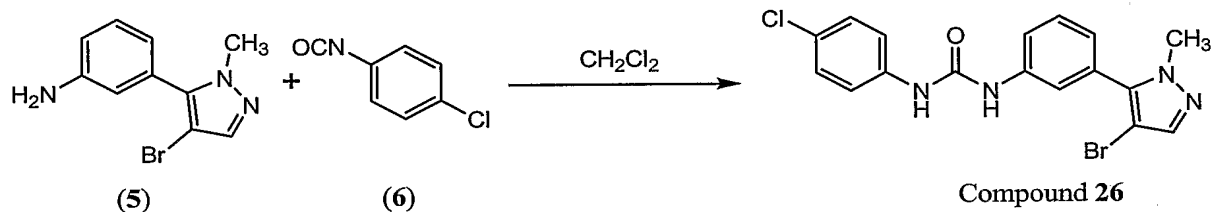
Scheme 4



Step (iv)



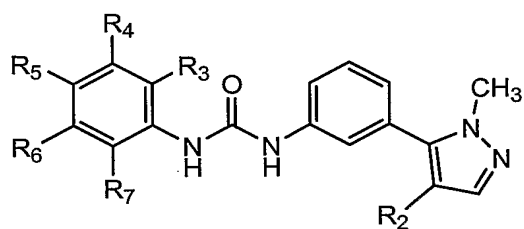
Step (v)



5

Representative activities for the 5-HT_{2A} modulators of the present invention are shown in Table 1, *infra*; see Examples 1-4 for description:

TABLE 1



Compound No.	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	IC ₅₀ (nM) IP Accumulation
9	Cl	H	F	F	H	H	18
10	Cl	F	H	H	F	H	37
11	Cl	H	F	H	F	H	46
12	Cl	H	Cl	F	H	H	23
13	Cl	F	H	F	H	H	25

14	Cl	F	F	F	H	H	48
15	Cl	CF ₃	H	F	H	H	158
16	Cl	H	CF ₃	F	H	H	45
17	Br	F	H	F	H	H	14
18	Br	H	F	F	H	H	28
19	Br	H	F	H	F	H	79
20	Br	H	Cl	F	H	H	17
21	Br	CF ₃	H	F	H	H	69
22	Br	H	CF ₃	F	H	H	11
23	Br	F	F	F	H	H	19
24	Br	CF ₃	H	Cl	H	H	34
25	Br	H	CF ₃	Cl	H	H	27
26	Br	H	H	Cl	H	H	8
27	Br	H	H	F	H	H	6

DEFINITIONS

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control.

AGONISTS shall mean moieties that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

PARTIAL AGONISTS shall mean moieties which activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists.

ANTAGONIST shall mean moieties that competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. **ANTAGONISTS** do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

CANDIDATE COMPOUND shall mean a molecule (for example, and not limitation, a chemical compound) which is amenable to a screening technique.

COMPOSITION shall mean a material comprising at least two compounds or two components; for example, and not limitation, a Pharmaceutical Composition is a Composition.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity.

INHIBIT or **INHIBITING**, in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INVERSE AGONISTS shall mean moieties that bind the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

In addition to the foregoing beneficial uses for the modulators of 5HT2a receptor activity disclosed herein, the compounds disclosed herein are believed to be useful in the treatment of several additional diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include the following:

1. Antiplatelet Therapies (5HT2a mediated platelet aggregation):

Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or

stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

In a myocardial infarction (heart attack), the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 minutes), antiplatelets can reduce the damage to the heart.

A transient ischemic attack ("TIA" or "mini-stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation blood clots that cause first or second strokes.

Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrhythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly

irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the heart and traveling to the brain (embolism).

5HT2a receptors are expressed on smooth muscle of blood vessels and 5HT secreted by activated platelets causes vasoconstriction as well as activation of additional platelets during clotting. There is evidence that a 5HT2a inverse agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy. See Satimura, K, et al., Clin Cardiol **2002** Jan. 25 (1):28-32; and Wilson, H.C et al., Thromb Haemost **1991** Sep 2;66(3):355-60.

The 5HT2A inverse agonists disclosed herein provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limitation, the indications described above.

2. Asthma

It has been suggested that 5-HT (5-hydroxytryptamine) plays a role in the pathophysiology of acute asthma. See Cazzola, M. and Matera, M.G., TiPS, **2000**, 21, 13; and De Bie, J.J. et al., British J. Pharm., **1998**, 124, 857-864. The compounds of the present invention disclosed herein are useful in the prophylaxis or treatment of asthma, and the symptoms thereof.

3. Agitation

Agitation is a well-recognized behavioral syndrome with a range of symptoms, including hostility, extreme excitement, poor impulse control, tension and uncooperativeness (See Cohen-Mansfield J, and Billig, N., (1986), Agitated Behaviors in the Elderly. I. A Conceptual Review. J Am Geriatr Soc 34(10): 711-721).

Agitation is a common occurrence in the elderly and often associated with dementia such as those caused by Alzheimer's disease, Lewy Body, Parkinson's, and Huntington's, which are degenerative diseases of the nervous system and by diseases that affect blood vessels, such as stroke, or multi-infarct dementia, which is caused by multiple strokes in the brain can also induce dementia. Alzheimer's disease accounts for approximately 50 to 70% of all dementias (See Koss E, et al., (1997), Assessing patterns

of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 11(suppl 2):S45-S50).

5 An estimated five percent of people aged 65 and older and up to 20 percent of those aged 80 and older are affected by dementia. Of these sufferers, nearly half exhibit behavioral disturbances, such as agitation, wandering and violent outbursts.

Agitated behaviors can also be manifested in cognitively intact elderly people and by those with psychiatric disorders other than dementia

10 Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging evidence that agents acting at the 5HT2a receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I.R., et al., J Clin Psychiatry 1999 Feb., 60(2):107-115; and Street, J.S., et al., Arch Gen Psychiatry 2000 Oct., 57(10):968-976). The compounds of the invention disclosed herein are useful for treating agitation and symptoms thereof.

4. Add-on therapy to Haloperidol in the treatment of schizophrenia and other disorders:

20 Schizophrenia is a psychopathic disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by a number of characteristics, psychotic symptoms, progression, phasic development and deterioration in social behavior and professional capability in the region below the highest level ever attained. Characteristic psychotic symptoms are disorders of thought content (multiple, fragmentary, incoherent, implausible or simply delusional contents or ideas of persecution) and of mentality (loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (hallucinations), of emotions (superficial or inadequate emotions), of self-perception, of intentions and impulses, of interhuman relationships, and finally psychomotoric disorders (such as catatonia). Other symptoms are also associated with this disorder. (See, American Statistical and Diagnostic Handbook).

30 Haloperidol (Haldol) is a potent dopamine D2 receptor antagonist. It is widely prescribed for acute schizophrenic symptoms, and is very effective for the positive symptoms of schizophrenia. However, Haldol is not effective for the negative symptoms

of schizophrenia and may actually induce negative symptoms as well as cognitive dysfunction. In accordance with some methods of the invention, adding a 5HT_{2a} inverse agonist concomitantly with Haldol will provide benefits including the ability to use a lower dose of Haldol without losing its effects on positive symptoms, while reducing or eliminating its inductive effects on negative symptoms, and prolonging relapse to the patient's next schizophrenic event.

Haloperidol is used for treatment of a variety of behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS). Further uses include in the prophylaxis or treatment of infantile autism, huntington's chorea, and nausea and vomiting from chemotherapy and chemotherapeutic antibodies. Administration of 5HT_{2a} inverse agonists disclosed herein with haloperidol also will provide benefits in these indications.

For the prophylaxis or treatment of any of these 5HT_{2A} mediated diseases, compounds of Formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the prophylaxis or treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the prophylaxis or treatment of humans.

As indicated above, pharmaceutical compositions for treating 5-HT_{2A} mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active

ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to methods known in the art using those suitable dispersing or wetting agents and suspending agents, which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

5 Compounds of Formula (I) may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable nonirritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

10 Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

EXAMPLES

15 **Example 1**

General Screening Paradigm: Selection of Pre-Clinical Candidate Leads.

20 The “primary” screen designed to directly identify human 5HT_{2A}/5HT_{2C} receptor inverse agonists consisted of a membrane-based GTPγS binding assay utilizing membranes prepared from COS7 cells transiently transfected with the constitutively active human 5-HT_{2C} receptor. Candidate compounds (10μM final assay concentration) directly identified as inhibiting ligand-independent receptor-mediated increases in GTPγS binding by greater than 50-75% (arbitrary cut-off value) were considered active “hits”. Primary assay hits were then re-tested in the same assay to reconfirm their inverse agonist activity. If primary assay hits were reconfirmed active (50% or greater inhibition), and
25 therefore directly identified as, *e.g.*, an inverse agonist, so-called “directed libraries” could be created, *i.e.*, additional candidate compounds were synthesized based upon the structures of the reconfirmed hits (geared towards, *e.g.*, improvement in the characteristics of the compounds) whereby the directed library compounds were then evaluated for the ability to compete for radioligand binding to both mutant human 5HT_{2C}
30 (AP-1) and native 5-HT_{2C} receptors and radioligand binding to mutant and endogenous 5HT_{2A} receptors. Because these directed library candidate compounds were based upon

the structures of compounds that were directly identified from the membrane-based GTP γ S binding assay, the directed library compounds were not re-tested in the membrane-based GTP γ S binding assay but rather were then confirmed via the radioligand binding analyses. The radioligand binding analysis tests were initially performed at 10 μ M test compound in triplicate and if the compound inhibited radiolabeled binding by 50% or more, the analysis was followed by an eight concentration radioligand competitive binding evaluation (triplicate determinations at each test compound concentration) to determine K_i values. The last step in secondary assay evaluation was to determine if test compounds were capable of inhibiting ligand-independent mutant 5-HT_{2A} (AP-3) receptor-mediated accumulation of inositol phosphates (*e.g.*, IP, IP₂, IP₃). This evaluation involved initial testing of compound at 10 μ M in triplicate and if compound inhibited inositol phosphate accumulation by 50% or more, this analysis was followed by an eight concentration (triplicate determinations at each test compound concentration) IC₅₀ determination. This final assay confirms that the directly identified compounds retained inverse agonist properties.

Example 2

Constitutively Activated Human 5HT_{2C} Receptor (AP-1), Mediated Facilitation of GTP γ S Binding to COS7 Membranes.

Primary screening assays measuring GTP γ S binding to membranes prepared from COS7 cells transiently transfected with human mutated 5HT_{2C} receptor (AP-1) were used to directly identify inverse agonists in screening libraries (Tripos, Inc.). Candidate compound screens were performed in a total assay volume of 200 μ l using scintillant-coated Wallac ScintistripTM plates. The primary assay was comprised of the following chemicals (at indicated final assay concentrations): 20 mM HEPES, pH 7.4, 100 mM NaCl, 20 mM MgCl₂, 0.2% saponin, 0.2 mM ascorbic acid, 1 μ M GDP, 0.3 nM GTP γ ³⁵S, and 12.5 μ g of the above defined membranes. Incubations were performed for 60 minutes at ambient room temperature. The binding assay incubation was terminated by centrifugation of assay plates at 4,000 rpm for 15 minutes, followed by rapid aspiration of the reaction mixture and counting in a Wallac MicroBetaTM scintillation counter.

Primary screening of candidate compounds initially involved testing of 72 test compounds per assay plate (96-well plates were utilized), at a final assay concentration of 10 μ M candidate compound, in single replicates. A total of sixteen wells of each plate were dedicated for an eight-concentration clozapine (a confirmed 5HT_{2C}/2A inverse agonist) dose response curve (duplicate determinations at each concentration). Finally, a total of five assay wells of each plate were dedicated to define the negative control (AP-1 receptor expressing membranes without addition of candidate compounds) and three wells from each plate to define the positive control (membranes without AP-1 receptor).

Reconfirmation experiments involve re-testing candidate compounds in the same assay described above, except that candidate compounds were evaluated in triplicate, thus allowing evaluation of 24 compounds per 96-well assay plate. Similar to the primary assay plates, an eight-concentration clozapine dose response curve (duplicate determinations at each concentration) and the same negative and positive control wells were also included within each 96-well plate.

Example 3

Competition Studies for directly identified compounds: Mutated Human 5HT_{2C} Receptor (AP-1).

Radioligand binding competition experiments were performed in a total assay volume of 200 μ l using standard 96-well microtiter plates. The final assay ingredients consisted of assay buffer (20 mM HEPES and 10 mM MgCl₂), 1nM (³H)mesulergine, and 50 μ g of membranes (COS7 with AP-1 as defined above). Nonspecific (³H)mesulergine binding was defined in the presence of 100 μ M mianserin. Incubations were performed for 1 hour at 37°C. Receptor bound radioligand was resolved from free radioligand by rapid filtration of the assay mixture over a Wallac Filtermat™ Type B filter, followed by washing with ice-cold assay buffer using a Skatron™ cell harvester. Radioactivity was counted using a Wallac 1205 BetaPlate™ counter. Each assay plate contained five negative control wells (membranes expressing receptor and no candidate compound addition) and three positive control wells (each containing 100 μ M mianserin). For one-concentration tests, candidate compounds were diluted into assay buffer and screened at a final concentration of 10 μ M, in triplicate. For IC₅₀

determinations, candidate compounds were diluted in assay buffer and eight different concentrations were evaluated, in triplicate. A total of 16 wells were designated for an eight-concentration mianserin dose response curve evaluation for both assays. The same assay conditions were also used to evaluate competition of test compound for radioligand binding to membranes expressing native 5-HT_{2C} receptor.

Example 4

Competition Studies, Wild Type Human 5HT_{2A} Receptor.

Radioligand binding competition experiments were performed in a total assay volume of 200 µl using standard 96-well microtiter plates. The final assay ingredients comprised assay buffer (20 mM HEPES and 10mM MgCl₂), 1nM (³H)LSD, and 50 µg of the above-defined membranes (COS7 with AP-1). Nonspecific (³H)LSD binding was defined in the presence of 100 µM serotonin. Incubations were performed for 1 hour at 37° C.

Receptor bound radioligand was resolved from free radioligand by rapid filtration of the assay mixture over a Wallac Filtermat™ Type B filter, followed by washing with ice-cold assay buffer using a Skatron™ cell harvester. Radioactivity was counted using a Wallac 1205 BetaPlate™ counter. Each assay plate contained five negative control wells (membranes expressing receptor and no candidate compound addition) and three positive control wells (containing 100 µM mianserin). For one-concentration tests, candidate compounds were diluted into assay buffer and screened at a final concentration of 10 µM in triplicate. For IC₅₀ determinations, candidate compounds were diluted in assay buffer and eight different concentrations were evaluated in triplicate. A total of 16 wells were designated for an eight-concentration serotonin dose response curve evaluation for both assays. The same assay conditions were also used to evaluate competition of test compound for radioligand binding to membranes expressing native 5-HT_{2A} receptor.

SYNTHESIS

The following methods apply to synthesis disclosed herein: HPLC-method A:
Column: Luna C8, 150 x 4.6 mm, 3 µm SLC-56, with pre-column; Detection: 260 nm;
Temperature: 30 °C; Flow rate: 1.5 ml / min; Run time: 21 min; Post time: 8 min;

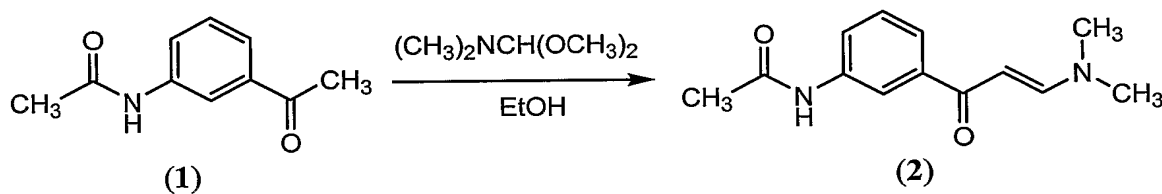
Injection volume: 5 μ l; Solvents: A: 5 mmol NH_4 -acetate in water, B: 5 mmol NH_4 -acetate in water / acetonitrile 2 : 8 (v/v); and

Time:	min.	% A
	0	80%
5	20	60%
	21	20%.

GC-method A: used specifically for Compounds (4), (5), (7), (8), Column: HP-5 (crosslinked Ph Me-siloxane); Initial temp.: 50 $^{\circ}\text{C}$; Initial time: 2 min; Heating rate: 10 $^{\circ}\text{C}$ / min; Final temp.: 250 $^{\circ}\text{C}$; and Final time: 10 min.

Example 5

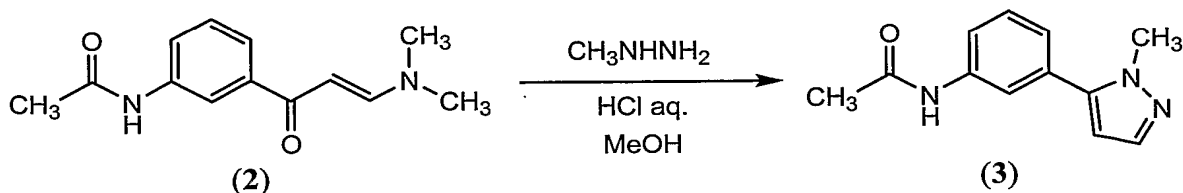
Synthesis of 3-Dimethylamino-1-((3'-acetamino)-phenyl)-2-propen-1-one (2) from 3-Acetamidoacetophenone (1):



3-Acetamidoacetophenone (5970 g, 33.7 mol) was placed in a reactor, followed by addition of N,N-dimethylformamide dimethylacetal (6445 g, 54.1 mol, 1.6 equivalents) and anhydrous ethanol (8103 g). The resulting mixture was heated to reflux (internal temp. = 79 to 76 $^{\circ}\text{C}$), whereupon a clear solution was formed. After 9 hours of reflux the conversion was complete (IPC: HPLC). After cooling to 0-5 $^{\circ}\text{C}$ within 1 to 2 hours it was stirred at this temperature overnight, filtered and washed with anhydrous ethanol (4330 g). The crystalline red material was dried in vacuum at 40 to 50 $^{\circ}\text{C}$ to afford enaminone 2 in a yield of 6237 g (80 %) and purity of 99.6 % (HPLC-method A).

Example 6

Synthesis of 5-(3-Acetamidophenyl)-1-methylpyrazole (3) from 3-Dimethylamino-1-((3'-acetamino)-phenyl)-2-propen-1-one (2):



The reactor was charged with methanol (12404 g) followed by methylhydrazine (1427 g, 31.0 mol, 1.16 equivalents). After cooling to 0 - 5 °C internal temp. 37 % aqueous HCl (8380 g, 85.0 mol, 3.2 equivalents) were added within 30 to 60 min. at an internal temp. of < 10 °C. After cooling to - 10 to 0 °C a suspension of 3-(dimethylamino)-1-(3'-acetamino)-phenyl-2-propen-1-one (6200 g, 26.7 mol) in methanol (44900 g) was added within 45 to 75 min. at an internal temp. of 0 to -10 °C. After completed addition it was warmed to 10 to 15°C within 30 to 60 min. and held for 2 hours at this temp., whereupon less of 1 % of the starting material could be detected by HPLC, a yellow suspension was obtained. Then 25 % aqueous ammonia (4752 g, 69.7 mol) were added within 20 to 40 min., forming a clear orange-colored reaction-mixture (pH 8.1). It was warmed up to 25 to 40 °C of internal temperature and 41.37 kg of solvent were distilled off during 4 to 7 hours, whereupon the product began to crystallize. After cooling to internal temp. = 20 to 30 °C within 45 to 75 min. water (24.90 kg) was added within 10 to 30 min. at int. temp. of 20 to 30°C. It was cooled down to 0 to 5°C within 1 to 2 h and stirred over night (13 h) at this temperature, followed by filtration. The product was washed with pre-cooled water (9270 g). The wet product was dried in vacuum (45 to 60°C) to yield 4938 g (86%) of desired 5-(3-acetamidophenyl)-1-methylpyrazole, purity 99.9 % (HPLC-method A). ¹H NMR (300 MHz, CDCl₃) δ 9.42 (s, 1H); 7.79 (d, J= 1.2 Hz, 1H); 7.58 (d, J 8.3 Hz, 1H); 7.47 (d, J= 1.9 Hz, 1H); 7.36 (dd, J= 7.5,8.3 Hz, 1H); 7.11 (dd, J= 1.2,7.5 Hz, 1H); 6.29 (d, J= 1.9 Hz, 1H); 3.90 (s, 3H); 2.16 (s, 3H).

Representative isomer ratios are shown in **TABLE 2** utilizing various reaction conditions.

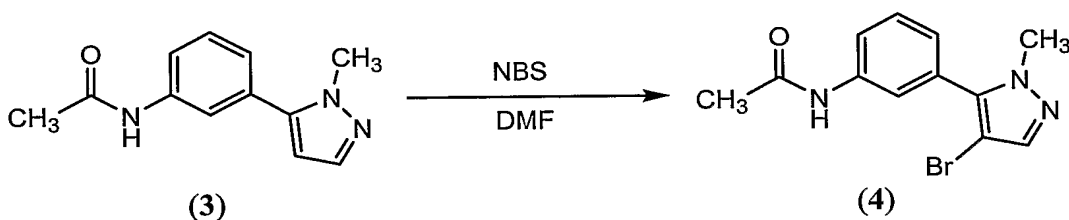
TABLE 2

Exper. No.	Enaminone (mmol)	Solvent (grams)	Equivalents HCl	Equivalents CH ₃ NHNH ₂	Temperature (°C)	Isomer Ratio 1-Methyl (3):2-Methyl Pyrazole*
1	4.1	1.0 g HOAc 6.4 g MeOH	0	1.16	0 to RT	53:47
2	4.1	4.0 g MeOH	1.5	1.16	0 to RT	82:18
3	4.1	4.0 g MeOH	3.0	1.16	RT to 35	82:18
4	12.3	12.0 g MeOH	3.2	1.16	0 to RT	88:12
5	4.1	10.0 g EtOH	3.2	1.16	0 to RT	88:12
6	4.3	4.0 g MeOH	3.0	1.12	0 to RT	88:12
7	172	640.0 g MeOH	3.2	1.16	0 to RT to 40	86:14
8	4.3	17.0 g MeOH	6.0	1.12	0 to RT	91:9

* Isomer Ratios are given as area % determined by HPLC at 250 nm

5 Example 7

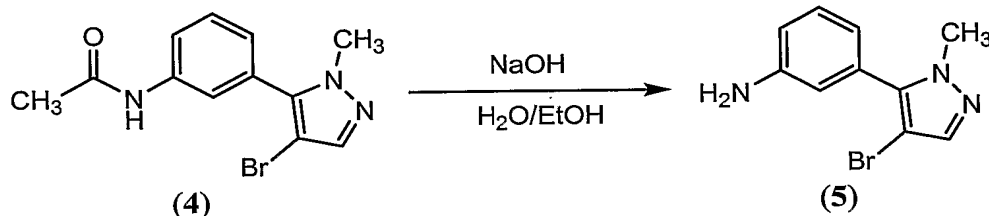
Synthesis of 5-(3-Acetamidophenyl)-4-bromo-1-methylpyrazole (4) from 5-(3-Acetamidophenyl)-1-methylpyrazole (3)



The reactor was charged with 5-(3-acetamidophenyl)-1-methylpyrazole (1135 g, 5.27 moles) that was suspended in N,N-dimethylformamide (2855 g). A solution of N-bromosuccinimide (963 g, assay 97 %, 5.25 moles) in N,N-dimethylformamide (1870 g) was added at 20 to 30 °C within 40 to 80 min. (IPC 1 hour after addition showed completed reaction). Within 30 to 60 min. it was warmed up to 50 to 60 °C and water (9743 g) was added within 30 to 60 min. at int. temp. = 50 to 60 °C. It was cooled down to 0 to 5°C within 2 to 3 h and held at this temp. for 30 to 60 min., followed by filtration and washing of the crystalline material with water (5286 g). The product was dried in vacuum (50 to 60 °C), yielding 1432 g (92 %) of the 5-(3-acetamidophenyl)-4-bromo-1-methylpyrazole, purity 99.2 % (HPLC-method A).

Example 8

Synthesis of 5-(3-aminophenyl)-4-bromo-1-methylpyrazole (**5**) from 5-(3-Acetamidophenyl)-4-bromo-1-methylpyrazole (**4**):



The reactor was charged with 5-(3'-acetaminophenyl)-4-bromo-1-methyl-1*H*-pyrazole **4** (184 g, 0.62 mol), followed by ethanol (464 g) and aqueous NaOH solution (30% by weight) (414 g, 3.10 mol, 5 equivalents). It was heated to reflux whereupon an emulsion was formed. After 17 h of reflux HPLC-analysis showed complete consumption of starting material. It was cooled to an internal temp. of 50 to 70 °C and ethanol was evaporated under reduced pressure until 603 g of reaction mixture were left. Diisopropyl ether (1446 g) was added and after stirring for 30 to 60 min. at an internal temp. of 55 to 60 °C the phases were separated. The organic layer was cooled down to 0 - 5 °C with stirring within 1 to 2 h and seeded at 44 °C. It was stirred for further 30 to 60 min. at 0 to 5 °C and filtered. The product was dried in vacuum at 40 to 50 °C, yielding 96.8 g (61 %) of 5-(3-aminophenyl)-4-bromo-1-methylpyrazole, purity 98.1 % (HPLC-method A). By evaporation of the mother liquor a second crop of product (55 g, 35 %) could be isolated. Thus a total yield of 96 % has been obtained. ¹H NMR (300 MHz, CDCl₃) δ 7.51 (s 1H); 7.26 (dd; J 7.8 Hz, 1H); 6.72 - 6.77 (m, 2H); 6.68 (dd; J 1.8 Hz, 1H); 3.80 (s, 3H).

Shown in **TABLE 3** is the time course for the acid hydrolysis of 5-(3-Acetamidophenyl)-4-bromo-1-methylpyrazole (**4**) to 5-(3-aminophenyl)-4-bromo-1-methylpyrazole (**5**). The reaction was conducted as follows: a mixture of 5-(3-acetamidophenyl)-4-bromo-1-methylpyrazole (**4**) as the hydrobromide (1.50 g, 4.0 mmol), conc HCl (0.80 g, 8 mmol) in ethanol (3.1 g) and water (1.4 g) was heated to reflux. Samples were taken at various time points and analyzed by HPLC.

TABLE 3

Time (hr)	Starting Material Compound (4) (%)	Product Compound (5) (%)	Unbrominated Amine (%)	Dibrominated Amine (Minor Isomer, %)	Dibrominated Amine (Major Isomer, %)
1	7.7	85.5	1.7	0.6	2.1
2	0.9	89.7	2.9	0.9	3.0
3	0.4	88.4	3.8	1.2	3.5
4	0.4	86.4	4.7	1.4	4.2
6	0.4	83.0	6.3	1.9	5.3
21	0.3	45.5	22.8	5.1	17.3

In a similar manner, a time course was determined for alkaline hydrolysis. The data are shown in **TABLE 4**. The reaction was conducted as follows: a mixture of 5-(3-acetamidophenyl)-4-bromo-1-methylpyrazole (**4**) as the hydrobromide (1.50 g, 4.0 mmol) and 30% aqueous NaOH (2.60 g, 20 mmol) in ethanol (3.0 g) and water (1.25 g) was heated to reflux. Samples were taken at various time points and analyzed by HPLC.

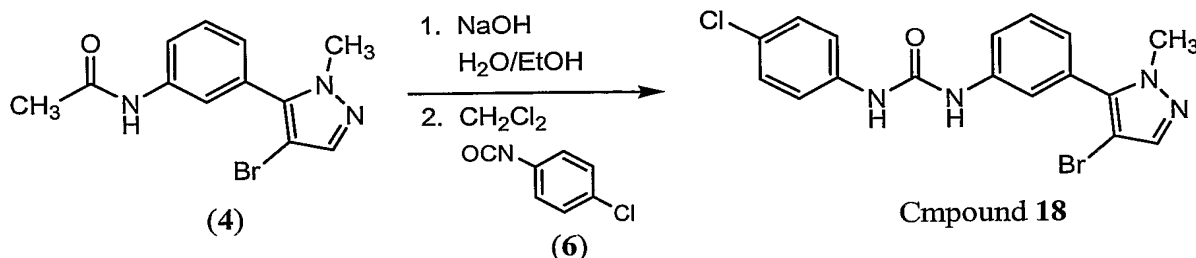
TABLE 4

Time (hr)	Starting Material Compound (4) (%)	Product Compound (5) (%)	Unbrominated Amine (%)	Dibrominated Amine (Minor Isomer, %)	Dibrominated Amine (Major Isomer, %)
2.5	50.3	47.4	1.0	0	0
5	23.0	74.7	1.6	0	0
22	1.2	95.9	2.3	0	0

As related to the study shown in **TABLE 3** and **TABLE 4**, the starting material, Compound (**4**), contained an impurity as the unbrominated amine.

Example 9

Synthesis of N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino) carboxamide (Compound 26, Table 1) from 5-(3-Acetamidophenyl)-4-bromo-1-methylpyrazole (**4**):

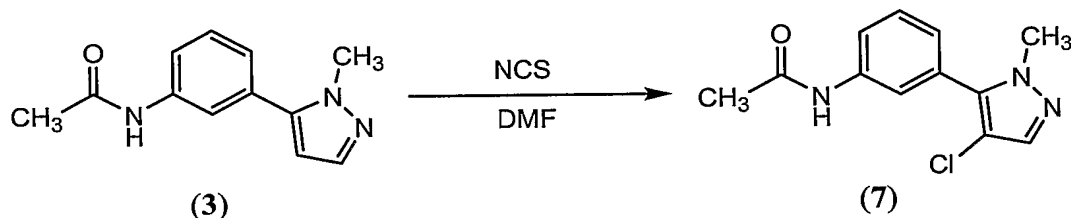


The reactor was charged with 5-(3'-acetaminophenyl)-4-bromo-1-methyl-1H-pyrazole 4 (1189 g, 4.04 mol), followed by ethanol (2980 g) and aqueous NaOH solution (30% by weight) (2685 g, 20.1 mol, 5 equivalents). It was heated to reflux whereupon an emulsion was formed. After 16 h HPLC-analysis revealed consumption of starting material. It was cooled to an internal temp. of 40 to 50 °C and ethanol was evaporated under reduced pressure until 1420 g of reaction mixture were left. It was seeded with 5-(3-aminophenyl)-4-bromo-1-methylpyrazole (5) and cooled to 20 to 25 °C. The crude product (5) was filtered by suction and washed with water (2 x 2300 g). The wet product (5) was dissolved in dichloromethane (7475 g). After 10 to 15 min. stirring was stopped and the emulsion was allowed to separate in two phases (10 to 15 min.). The organic layer was isolated and anhydrous sodium sulfate (412 g) was added. It was stirred for 10 to 20 min., filtered by suction and washed with dichloromethane (4672 g). To this solution a mixture of 4-chlorophenyl-isocyanate (646 g; 4.20 mol, 1.04 equivalents) and dichloromethane (1645 g) was added within 10 to 20 min. at 20 to 25 °C. After 5 h the suspension of product obtained was cooled to 0 - 5 °C and stirred for further 40 to 80 min. at this temperature. It was filtered by suction (1.5 h necessary) and washed with dichloromethane (3211 g). The product was dried at 40 to 45 °C, yielding 1260 (77 %) of Compound 18, purity 98.9 % (HPLC-method A).

¹H NMR (300 MHz, DMSO-d₆) δ 8.92 (s, 1H); 8.89 (s, 1H); 7.65 (s, 1H); 7.63 - 7.62 (dd, J = 1.4, 2.0 Hz, 1H); 7.59 - 7.55 (ddd, J = 1.2, 2.0, 8.2 Hz, 1H); 7.54 - 7.49 (m, J = 8.9 Hz, 2H); 7.49 - 7.43 (dd, J = 7.6, 8.2 Hz, 1H); 7.35 - 7.30 (m, J = 8.9 Hz, 2H); 7.11 - 7.08 (ddd, J = 1.2, 1.4, 7.6 Hz, 1H), 3.79 (s, 3H). ¹³C-NMR (300 MHz, DMSO-d₆): δ 152.3; 140.3; 139.8; 138.4; 129.1; 128.5; 128.2; 125.4; 123.0; 119.8; 119.2; 118.9; 92.2; 38.1.

Example 10

Synthesis of 5-(3'-acetylaminophenyl)-4-chloro-1-methyl-1*H*-pyrazole (7) from 5-(3'-acetaminophenyl)-1-methyl-1*H*-pyrazole 3:

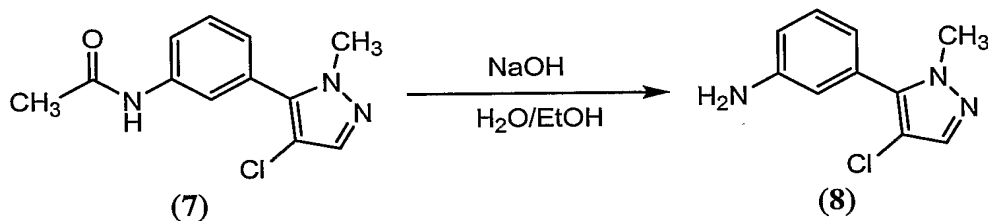


The reactor was charged with 5-(3'-acetaminophenyl)-1-methyl-1*H*-pyrazole 3 (363.6 g, 1.69 mol) that was suspended in N,N-dimethylformamide (911 g). A solution of N-chloro-succinimide (230.2 g, assay 98 %, 1.69 mol) in N,N-dimethylformamide (750 g) was added at an internal temp. of 51 to 57 °C during a period of 1 to 1.5 h. After stirring for further 2 to 3 h at 53 to 63 °C IPC showed absence of starting material. To the clear solution water (4811 g) was added within 30 to 60 min. at an internal temp. of 55 to 60 °C, followed by cooling to int. temp of 0 to 5 °C within 2 to 3 h. After stirring for further 30 to 60 min. at this temperature it was filtered and washed with water (1689 g). The product was dried in vacuum (50 to 60 °C), yielding 400 g (96%) of the chloro-pyrazole 7 (purity 100 %, HPLC-method AR116081).

¹H NMR (300 MHz, CDCl₃) δ 8.05 (s, 1H); 7.64 (s, 1H), 7.58 (d, J 8.4 Hz, 1H), 7.49 (s, 1H), 7.42 (dd, J 7.6, 8.4 Hz, 1H), 7.14 (d, J 7.6 Hz, 1H), 3.79 (s, 3H), 2.18 (s, 3H).

Example 11

Synthesis of 5-(3'-aminophenyl)-4-chloro-1-methyl-1*H*-pyrazole (8) from 5-(3'-acetylaminophenyl)-4-chloro-1-methyl-1*H*-pyrazole (7):

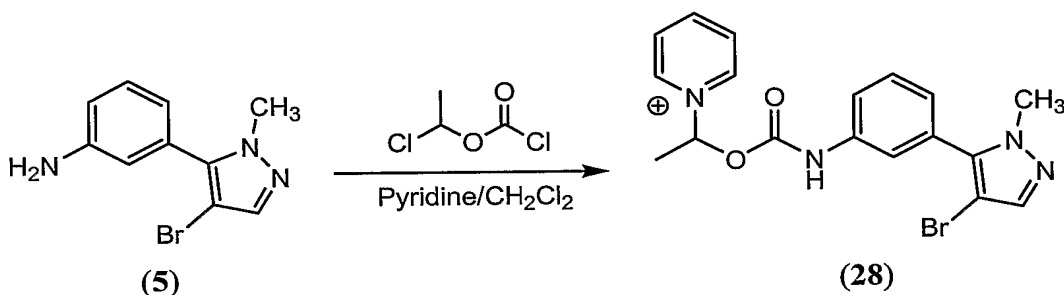


The reactor was charged with 5-(3'-acetaminophenyl)-4-chloro-1-methyl-1*H*-pyrazole 7 (397 g, 1.59 mol) followed by ethanol (995 g) and aqueous NaOH solution (30% by weight) (1056 g, 7.92 mol, 5 equivalents). It was heated to reflux whereupon a yellowish emulsion was formed. After 5.2 h of reflux HPLC analysis showed

consumption (< 0.5 % left) of starting material. It was cooled to an internal temp. of 50 to 70 °C and ethanol was evaporated at a pressure of 90 to 130 mbar until 1462 g of reaction mixture were left. Diisopropyl ether (684 g) was added with efficient stirring , after separation of phases the aqueous layer was retransferred into the reactor and again extracted with diisopropyl ether (150 g). Both organic layers were combined and seeded followed by cooling of the suspension to - 8 to -12 °C of internal temp. within 1 to 2 h. It was stirred over night at this temperature. The product was filtered and dried over night in vacuum at 40 to 50 °C, yielding 168.4 g (51 %) of the amine **8**.

Example 12

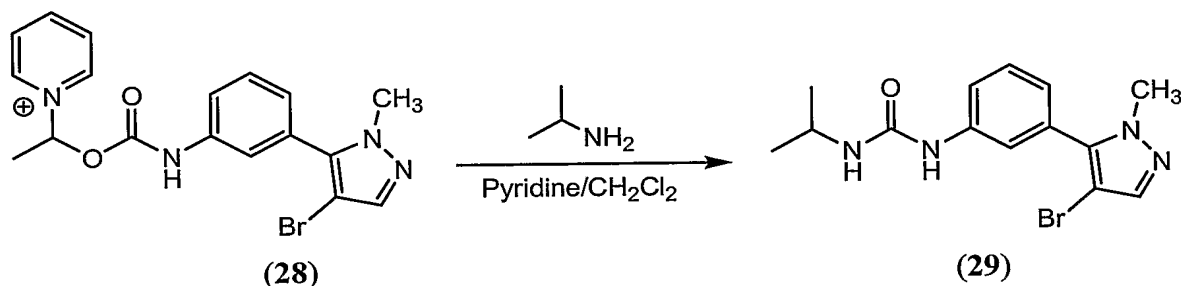
Synthesis of Pyridinium Salt (**28**) from 5-(3-aminophenyl)-4-bromo-1-methylpyrazole (**5**):



Pyrazole (**5**) (3.07g, 12.2 mmol) was dissolved in anhydrous CH₂Cl₂ (45 mL) and treated with pyridine (2.96 mL, 36.6 mmol). The solution was stirred at room temperature. After allowing it to stir for five minutes, 1-chloroethyl chloroformate (1.45 mL, 13.4 mmol) was added drop by drop. After 4.5 hours at room temperature, the reaction was shown to be incomplete by TLC and LC/MS. An additional equivalent of the chloroformate (1.32 mL, 12.2 mmol) was added. Once the reaction went to completion (after another two hours,) it was worked up with EtOAc (2 x 100 mL) and Brine (2 x 100 mL). Upon being treated to this work up, the pyridinium salt precipitated out of solution into the aqueous layer in a 57-80% yield: LCMS m/z (%) = 401 (M+H⁷⁹Br, 14), 403 (M+H⁸¹Br, 10). ¹H NMR (400 MHz, CD₃OD) δ 9.27 (d, 2H), 8.71 (t, 1H), 8.23 (t, 2H), 7.52 (s, 1H), 7.50 (s, 1H), 7.47 (t, 1H), 7.15 (d, 1H), 7.11 (q, 1H), 3.76 (s, 3H), 2.03 (d, 3H).

Example 13

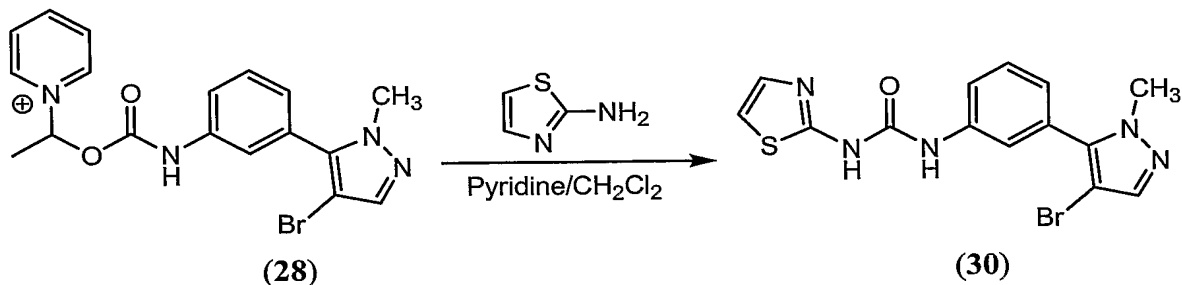
Synthesis of N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)(isopropylamino) carboxamide (29) from pyridinium salt (28):



Pyridinium salt (2), from Example 12, was dissolved in anhydrous CH₂Cl₂ (3 mL). The solution was stirred and treated with pyridine (118 μ L, 1.46 mmol). The solution was stirred at room temperature for five minutes. Then the solution was heated to 39°C and isopropylamine (45.5 μ L, 0.53 mmol) was added drop by drop. After two hours the reaction was complete. The reaction mixture was quenched with 5 mL 1N HCl and the organic layer was extracted with EtOAc. The organic layer was then dried with Na₂SO₄, filtered and the solvent was removed under reduced pressure, yielding 40.1 mg (24%) of AR145253: LCMS m/z (%) = 337 (M+H⁷⁹Br, 100), 339 (M+H⁸¹Br, 90). ¹H NMR (400 MHz, CDCl₃) σ 7.53 (s, 1H), 7.43 (m, 3H), 7.08 (d, 1H), 4.02 (m, 1H), 3.83 (s, 3H), 1.20 (d, 6H).

Example 14

Synthesis of N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)(thiazol-2-yl amino) carboxamide (30) from pyridinium salt (28):

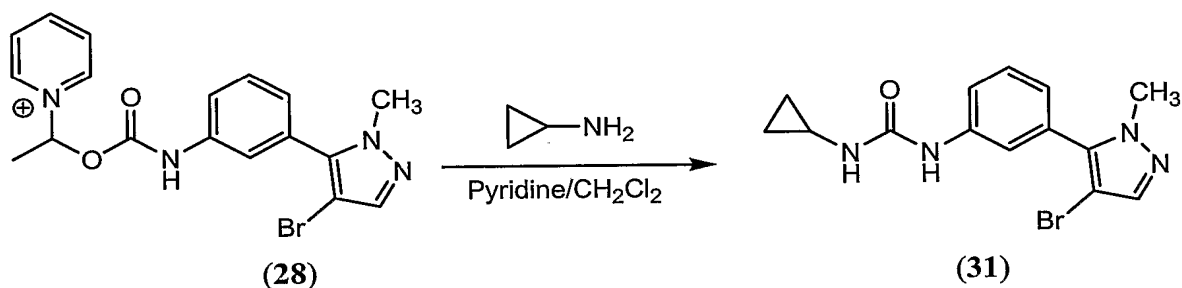


Pyridinium salt (28), from Example 12, was treated with 2-Aminothiazole, in a similar manner to as described in Example 12 for N-(3-(4-bromo-2-methylpyrazole-3-

yl)phenyl)(isopropylamino) carboxamide (29), to provide N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)(thiazol-2-yl amino) carboxamide in a yield of 22%: LCMS m/z (%) = 380 ($M+H^{81}Br$, 100), 378 ($M+H^{79}Br$, 72). 1H NMR (400MHz. $CDCl_3$) σ 7.72 (d,1H), 7.60 (d,1H), 7.48 (d,1H), 7.44 (s, 1H), 7.31 (s, 1H), 7.22 (t,1H), 7.07 (d, 1H), 3.83 (s, 3H).

Example 15

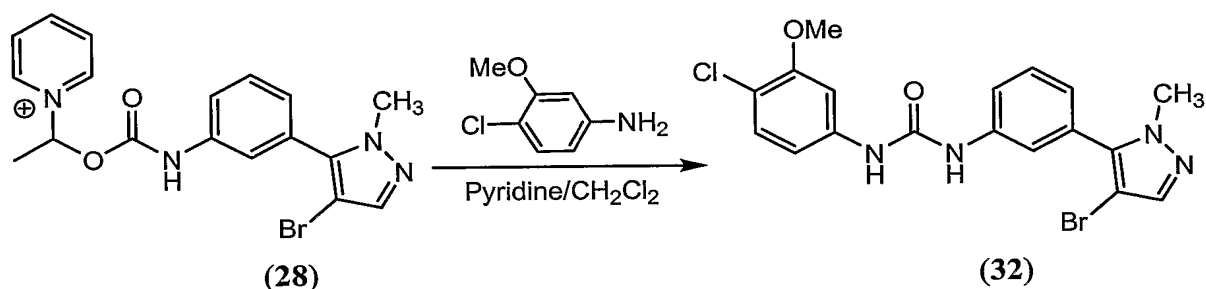
Synthesis of N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)(cyclopropylamino) carboxamide (31) from pyridinium salt (28):



Pyridinium salt (28), from Example 12, was treated with cyclopropyl amine, in a similar manner as described in Example 12, to provide N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)(cyclopropylamino) carboxamide in a yield of 22%: LCMS m/z (%) = 337 ($M+H^{79}Br$, 100), 339 ($M+H^{81}Br$, 97). 1H NMR (400MHz. $CDCl_3$) σ 7.55 (d, 1H), 7.47 (s, 1H), 7.465 (s, 1H), 7.461 (t, 1H), 7.10 (d, 1H), 3.84 (s, 3H), 0.88 (m, 2H), 0.67 (m, 2H).

Example 15

Synthesis of N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)((4-chloro-3-methoxyphenyl)amino) carboxamide (32) from pyridinium salt (28):



Pyridinium salt (28), from Example 12, was treated with 4-chloro-3-methoxyaniline, in a similar manner to as described in Example 12, to provide N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)((4-chloro-3-methoxyphenyl)amino) carboxamide in a yield of 60%: LCMS m/z (%) = 435 (M+H⁷⁹Br, 97), 437 (M+H⁸¹Br, 100).

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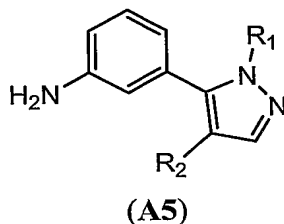
Throughout this application, various publications, patents and published patent applications are cited. The disclosures of these publications, patents and published patent applications referenced in this application are hereby incorporated by reference in their entirety into the present disclosure. Modifications and extension of the disclosed inventions that are within the purview of the skilled artisan are encompassed within the above disclosure and the claims that follow.

10

CLAIMS

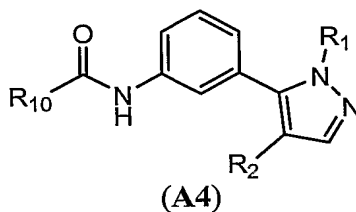
We Claim:

1. A process for making a compound of Formula (A5):



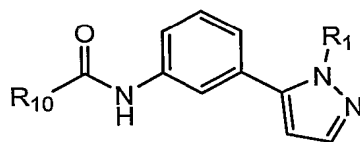
the process comprising:

hydrolyzing a compound of Formula (A4):



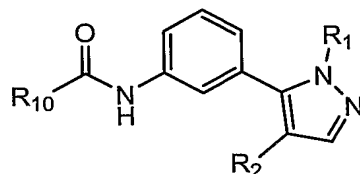
with an alkali metal hydroxide in an hydrolyzing solvent to yield a compound of Formula (A5); wherein R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; and R₁₀ is C₁₋₆ alkyl.

2. The process according to claim 1 wherein the alkali metal hydroxide is sodium hydroxide.
3. The process according to claim 2 wherein the hydrolyzing solvent is aqueous ethanol.
4. The process according to claim 3 wherein the hydrolyzing step is conducted at a temperature between about 60°C to about 80°C.
5. The process according to claim 1 comprising the steps of:
halogenating a compound of Formula (A3)



(A3)

with a halogenating reagent in a halogenating solvent to yield a compound of Formula (A4);

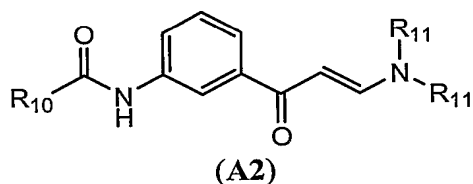


(A4)

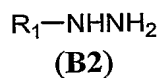
; and

hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5); wherein R₁₀ is C₁₋₆ alkyl.

6. The process according to claim 5 wherein the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide.
7. The process according to claim 6 wherein the halogenating reagent is N-bromosuccinimide and the halogenating solvent is N,N-dimethylformamide, and the halogenating step is conducted at a temperature between about 20°C to about 60°C.
8. The process according to claim 7 wherein the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted at a temperature between about 60°C to about 80°C.
9. The process according to claim 1 comprising the steps of:
cyclizing a compound of Formula (A2):

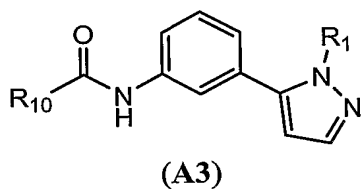


with a compound of Formula (B2):



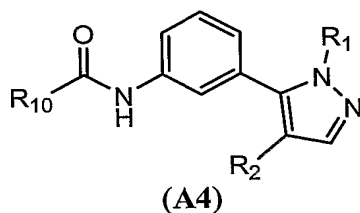
R_1 is C_{1-2} alkyl;

the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (A3);



; and

halogenating a compound of Formula (A3) with a halogenating reagent in a halogenating solvent to yield a compound of Formula (A4);



;

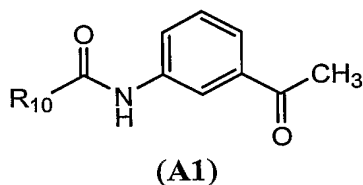
hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5); wherein R_1 is C_{1-2} alkyl; R_{10} is C_{1-6} alkyl; and R_{11} is C_{1-3} alkyl.

10. The process according to claim 9 further comprising a cyclizing acid in the cyclizing step.

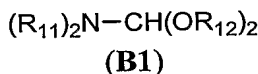
11. The process according to claim 10 wherein the cyclizing acid is hydrochloric acid.

12. The process according to claim 11 wherein the compound of Formula (B2) is methyl hydrazine.

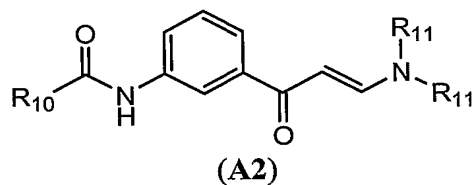
13. The process according to claim 12 wherein the cyclization solvent is methanol.
14. The process according to claim 13 wherein the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide, the halogenating solvent is N,N-dimethylformamide, and the halogenating step is conducted at a temperature between about 20°C to about 60°C.
15. The process according to claim 14 wherein the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted at a temperature between about 60°C to about 80°C.
16. The process according to claim 1 comprising the steps of:
condensing a compound of Formula (A1):



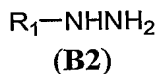
with a compound of Formula (B1):



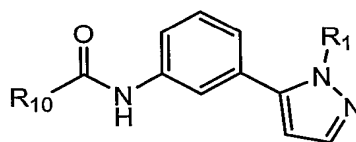
the condensing step is optionally conducted in an condensing solvent to yield a compound of Formula (A2):



cyclizing a compound of Formula (A2) with a compound of Formula (B2):



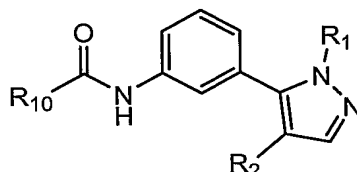
the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (A3):



(A3)

;

halogenating a compound of Formula (A3) with a halogenating reagent in a halogenating solvent to yield a compound of Formula (A4);



(A4)

; and

hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5); wherein R₁ is C₁₋₂ alkyl; R₁₀ is C₁₋₆ alkyl, R₁₁ is C₁₋₃ alkyl; and R₁₂ is C₁₋₆ alkyl or alkylaryl; or both R₁₂ groups together form a 5 or 6 membered heterocyclic ring.

17. The process according to claim 16 wherein the compound of Formula (B1) is *N,N*-dimethylformamide dimethyl acetal.
18. The process according to claim 17 wherein the condensing solvent is ethanol and the condensing step is conducted at a temperature of about 25°C to about 95°C.
19. The process according to claim 18 wherein the condensing step is conducted at a temperature of about 70°C to about 80°C.
20. The process according to claim 19 further comprising a cyclizing acid in the cyclizing step and the cyclizing acid is hydrochloric acid.
21. The process according to claim 20 wherein the compound of Formula (B2) is methyl hydrazine and the cyclization solvent is methanol.

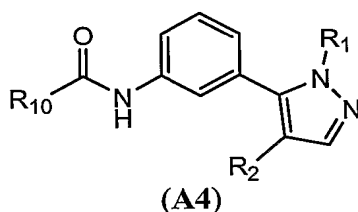
22. The process according to claim 21 wherein the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide, the halogenating solvent is N,N-dimethylformamide, and the halogenating step is conducted at a temperature between about 20°C to about 60°C.

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23. The process according to claim 22 wherein the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted at a temperature between about 60°C to about 80°C.

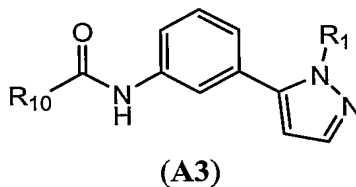
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24. A process for making a compound of Formula (A4):



the process comprising the steps of:

halogenating a compound of Formula (A3)



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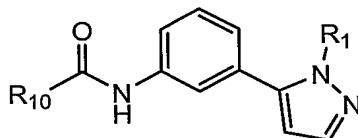
with a halogenating reagent in a halogenating solvent to yield the compound of Formula (A4); wherein R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; and R₁₀ is C₁₋₆ alkyl.

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25. The process according to claim 24 wherein the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide.
26. The process according to claim 25 wherein the halogenating reagent is N-bromosuccinimide and the halogenating solvent is N,N-dimethylformamide.

27. The process according to claim 26 wherein the halogenating step is conducted at a temperature between about 20°C to about 60°C.

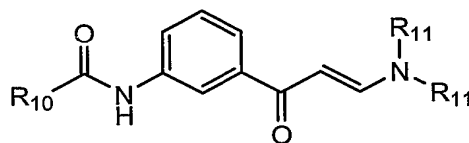
28. A process for making a compound of Formula (A3):



(A3)

the process comprising the steps of:

cyclizing a compound of Formula (A2):



(A2)

with a compound of Formula (B2):



(B2)

the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (A3); wherein R₁ is C₁₋₂ alkyl; R₁₀ is C₁₋₆ alkyl; and R₁₁ is C₁₋₃ alkyl.

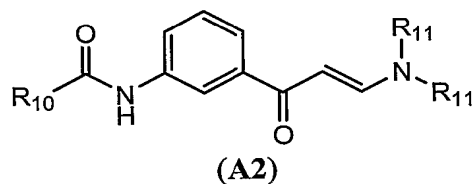
29. The process according to claim 28 further comprising a cyclizing acid in the cyclizing step.

30. The process according to claim 29 wherein the cyclizing acid is hydrochloric acid.

31. The process according to claim 30 wherein the compound of Formula (B2) is methyl hydrazine.

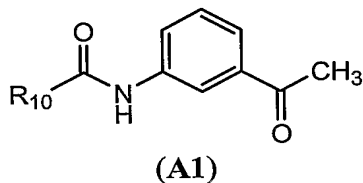
32. The process according to claim 31 wherein the cyclization solvent is methanol.

33. A process for making a compound of Formula (A2):

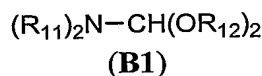


the process comprising the steps of:

condensing a compound of Formula (A1):



with a compound of Formula (B1):

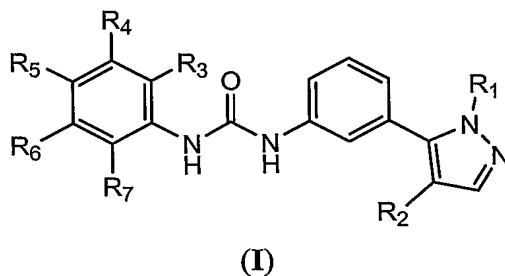


the condensing step is optionally conducted in an condensing solvent to yield a compound of Formula (A2); wherein R_{10} is C_{1-6} alkyl; R_{11} is C_{1-3} alkyl; and R_{12} is C_{1-6} alkyl or alkylaryl; or both R_{12} groups together form a 5 or 6 membered heterocyclic ring.

34. The process according to claim 33 wherein the compound of Formula (B1) is *N,N*-dimethylformamide dimethyl acetal.

35. The process according to claim 34 wherein the condensing solvent is ethanol and the condensing step is conducted at a temperature of about 25°C to about 95°C.

36. A process for making a compound of Formula (I):



wherein:

R_1 is C_{1-2} alkyl;

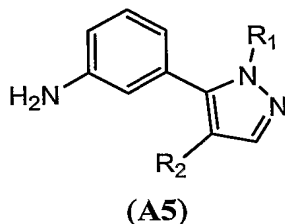
R_2 is Cl or Br; and

R_3, R_4, R_5, R_6 and R_7 are each independently selected from H,

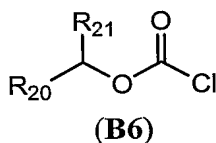
halogen, or haloalkyl; provided that at least one is not H;

the process comprising:

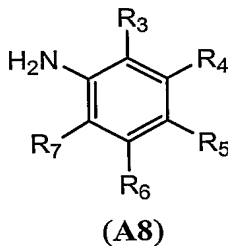
reacting a compound of Formula (A5):



with a substituted alkyl chloroformate of Formula (B6):



and an organic base in a non-reactive solvent to give an intermediate; and
coupling the intermediate with a compound of Formula (A8):

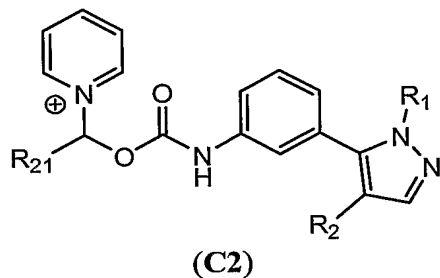


to yield the compound of Formula (I); wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; and wherein R_{20} is a Cl, Br, I, mesylate or tosylate; R_{21} is a C_1-C_8 alkyl.

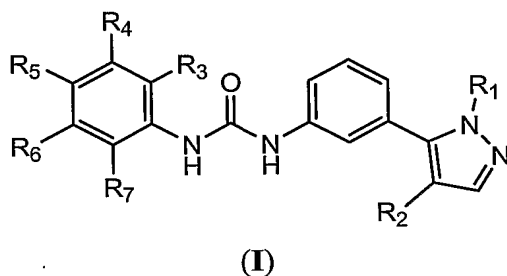
37. The process according to claim 36 wherein the organic base is pyridine.

38. The process according to claim 37 wherein the non-reactive solvent is methylene chloride.

39. The process according to claim 38 wherein the intermediate is Formula (C2):



40. A process for making a compound of Formula (I):



wherein:

R₁ is C₁₋₂ alkyl;

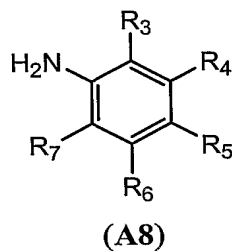
R₂ is Cl or Br; and

R₃, R₄, R₅, R₆ and R₇ are each independently selected from H,

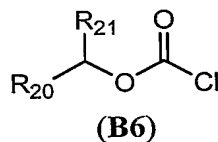
halogen, or haloalkyl; provided that at least one is not H;

the process comprising:

reacting a compound of Formula (A8):

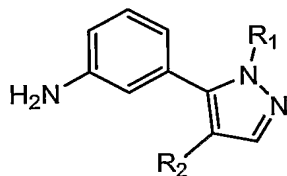


with a substituted alkyl chloroformate of Formula (B6):



wherein R₂₀ is a Cl, Br, I, mesylate or tosylate; R₂₁ is a C₁-C₈ alkyl;

and an organic base in a non-reactive solvent to give an intermediate; and coupling the intermediate with a compound of Formula (A5):



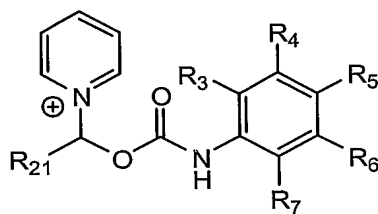
(A5)

to yield the compound of Formula (I); wherein R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; R₃, R₄, R₅, R₆ and R₇ are each independently selected from H, halogen, or haloalkyl; provided that at least R₃, R₄, R₅, R₆ and R₇ is not H.

41. The process according to claim 40 wherein the organic base is pyridine.

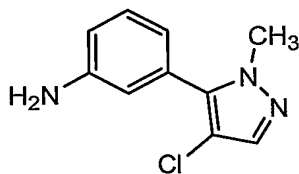
42. The process according to claim 41 wherein the non-reactive solvent is methylene chloride.

43. The process according to claim 42 wherein the intermediate is Formula (C4):

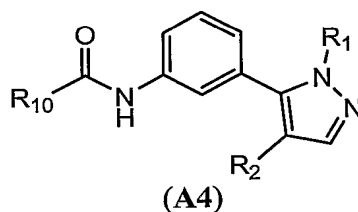


(C4)

44. A compound of the Formula:



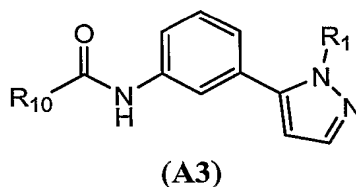
45. A compound of Formula (A4):



wherein R₁ is C₁₋₂ alkyl; R₂ is Cl or Br; and R₁₀ is C₁₋₆ alkyl.

46. The compound according to claim 45 wherein R₁ and R₁₀ are both CH₃, and R₂ is Br.

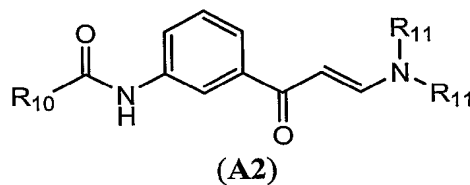
47. A compound of Formula (A3):



wherein R₁ is C₁₋₂ alkyl; and R₁₀ is C₁₋₆ alkyl.

48. The compound according to claim 47 wherein R₁ and R₁₀ are both CH₃.

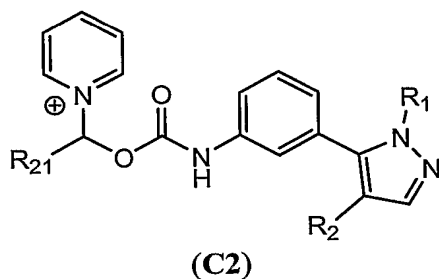
49. A compound of Formula (A2):



wherein R₁₀ is C₁₋₆ alkyl; and R₁₁ is C₁₋₃ alkyl.

50. The compound according to claim 49 wherein R₁₀ and R₁₁ are both CH₃.

51. A compound of the formula:



wherein:

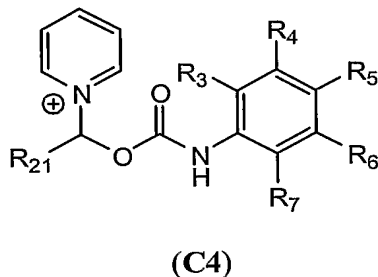
R_1 is C_{1-2} alkyl;

R_2 is Cl or Br; and

R_{21} is C_1-C_8 alkyl.

52. The compound according to claim 51 wherein R_1 is CH_3 ; R_2 is Br; and R_{21} is CH_3 .

53. A compound of the formula:



wherein R_3 , R_4 , R_5 , R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; and R_{21} is C_1-C_8 alkyl.

54. The compound according to claim 53 wherein R_3 , R_4 , R_5 , R_6 and R_7 are each independently selected from H, F or Cl; and R_{21} is CH_3 .

(19) World Intellectual Property
Organization
International Bureau



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(25) Filing Language: English

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(74) Agents: **CORUZZI, Laura, A.** et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).

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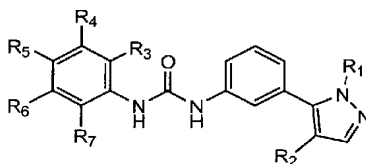
Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
7 October 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS OF MAKING PHENYLPYRAZOLES USEFUL AS SELECTIVE 5HT_{2A} MODULATORS AND INTERMEDIATES THEREOF



(I)

(57) Abstract: The present invention relates to a process for making certain selective 5HT_{2A} modulators of Formula (I) and the intermediates thereof: Formula (I) wherein R₁-R₇ are described. Compounds of Formula (I) are useful in the prophylaxis or treatment of 5HT_{2A} mediated diseases, such as, 5HT_{2A} mediated platelet aggregation, asthma, agitation, degenerative diseases of the CNS and the like.

WO 2004/028450 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/29736

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 231/16

US CL : 548/377.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/377.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,663,119 A (CHENE ET AL.) 02 September 1997 (02/09/97), see entire document, especially columns 1-2.	44



Further documents are listed in the continuation of Box C.



See patent family annex.

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later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

09 June 2004 (09.06.2004)

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/29736

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-23 and 44

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/29736

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Search Authority has found 7 inventions claimed in the International Application covered by the claims indicated below:

Group I, claim(s) 1-23 and 44, drawn to a process of making a compound of Formula (A5) and products.

Group II, claim(s) 24-27, 45 and 46, drawn to a process of making a compound of Formula (A4) and products.

Group III, claim(s) 28-32, 47 and 48, drawn to a process of making a compound of Formula (A3) and products.

Group IV, claim(s) 33-35, 49 and 50, drawn to a process of making a compound of Formula (A2) and products.

Group V, claim(s) 36-43, drawn to process of making a compound of Formula (I).

Group VI, claim(s) 51 and 52, drawn to a compound of (C2).

Group VII, claim(s) 53 and 54, drawn to a compound of (C4).

1. This International Searching Authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: each of the groups set forth above represents either a separate process or discrete heterocyclic or nonheterocyclic ring system which one skilled in the art which besides sharing no significant structural element, cannot be said to belong to a recognized class of chemical compounds. Accordingly, the unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper.

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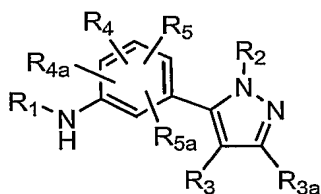
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(54) Title: DIARYLAMINE AND ARYLHETEROARYLAMINE PYRAZOLE DERIVATIVES AS MODULATORS OF 5HT_{2A}



(A)

(57) Abstract: One aspect of the present invention relates to certain diarylamine and arylheteroarylamine pyrazole derivatives of Formula (A) and pharmaceutical compositions that modulate the activity of the human 5HT_{2A} serotonin receptor. Compounds and pharmaceutical compositions are directed to methods useful in the prophylaxis or treatment of reducing platelet aggregation, sleep disorders, coronary artery disease, myocardial

infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia and related disorders. Another aspect of the present invention is directed to the method of prophylaxis or treatment of 5HT_{2A} serotonin receptor mediated disorders in combination with a dopamine D₂ receptor antagonist such as haloperidol, administered separately or together.



WO 2004/058722 A1

DIARYLAMINE AND ARYLHETEROARYLAMINE PYRAZOLE DERIVATIVES
AS MODULATORS OF 5HT_{2A}

FIELD OF THE INVENTION

One aspect of the present invention relates to certain diarylamine and arylheteroarylamine pyrazole derivatives as described herein and pharmaceutical compositions that modulate the activity of the human 5HT_{2A} serotonin receptor.

Compounds and pharmaceutical compositions are directed to methods useful in the prophylaxis or treatment of reducing platelet aggregation, sleep disorders, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia and related disorders. Compounds and pharmaceutical compositions are also directed to methods useful in cardioprotection, for example to protect against heart failure and the like; neuroprotection, for example to protect against strokes and the like; and diabetic neuropathy.

Another aspect of the present invention is directed to the method of prophylaxis or treatment of 5HT_{2A} serotonin receptor mediated disorders in combination with a dopamine D₂ receptor antagonist such as haloperidol, administered separately or together.

BACKGROUND OF THE INVENTION

Serotonin receptors

Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein-coupled receptors. Serotonin is thought to play a role in processes related to learning and memory, sleep, thermoregulation, mood, motor activity, pain, sexual and aggressive behaviors, appetite, neurodegenerative regulation, and biological rhythms. Not surprisingly, serotonin is linked to pathophysiological conditions such as anxiety, depression, obsessive-compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism, and neurodegenerative disorders. With respect to on anti-psychotic treatment approaches focused on the serotonin receptors, these types of therapeutics can generally be divided into two classes, the "typical" and the "atypical." Both have anti-psychotic effects, but the typicals also include concomitant motor-related side effects (extra pyramidal syndromes, *e.g.*, lip-smacking, tongue darting, locomotor movement, etc). Such side effects are thought to be associated with the compounds interacting

with other receptors, such as the human dopamine D2 receptor in the nigro-striatal pathway. Therefore, an atypical treatment is preferred. Haloperidol is considered a typical anti-psychotic, and clozapine is considered an atypical anti-psychotic.

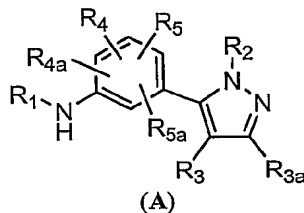
Serotonin receptors are divided into seven subfamilies, referred to as 5-HT1 through 5-HT7, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT2 subfamily is divided into three receptor subtypes: 5-HT2A, 5-HT2B, and 5-HT2C. The human 5-HT2C receptor was first isolated and cloned in 1987, and the human 5-HT2A receptor was first isolated and cloned in 1990. These two receptors are thought to be the site of action of hallucinogenic drugs. Additionally, antagonists to the 5-HT2A and 5-HT2C receptors are believed to be useful in treating depression, anxiety, psychosis, and eating disorders.

U.S. Patent Number 4,985,352 describes the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT1C receptor (now known as the 5-HT2C receptor). U.S. Patent Number 5,661,012 describes the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT2A receptor.

Mutations of the endogenous forms of the rat 5-HT2A and rat 5-HT2C receptors have been reported to lead to constitutive activation of these receptors (5-HT2A: Casey, C. *et al.* (1996) *Society for Neuroscience Abstracts*, 22:699.10, hereinafter "Casey"; 5-HT2C: Herrick-Davis, K., and Teitler, M. (1996) *Society for Neuroscience Abstracts*, 22:699.18, hereinafter "Herrick-Davis 1"; and Herrick-Davis, K. *et al.* (1997) *J. Neurochemistry* 69(3): 1138, hereinafter "Herrick-Davis-2"). Casey describes a mutation of the cysteine residue at position 322 of the rat 5-HT2A receptor to lysine (C322K), glutamine (C322Q), and arginine (C322R) which reportedly led to constitutive activation. Herrick-Davis 1 and Herrick-Davis 2 describe mutations of the serine residue at position 312 of the rat 5-HT2C receptor to phenylalanine (S312F) and lysine (S312K), which reportedly led to constitutive activation.

SUMMARY OF THE INVENTION

One aspect of the present invention pertains to certain diarylamine and arylheteroarylamine derivatives as shown in Formula (A):



wherein:

i) R_1 is aryl or heteroaryl optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-6} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide, C_{2-8} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl, thiol, nitro, phenoxy and phenyl; and wherein C_{2-6} alkenyl, C_{1-6} alkyl and C_{2-6} alkynyl substituents may be optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-6} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl, thiol and nitro; or two adjacent substituents together with the ring carbons to which they are bonded form a C_{5-7} cycloalkyl optionally replaced with 1 to 2 oxygen atoms;

ii) R_2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{3-7} cycloalkyl;

iii) R_3 is H, C_{2-6} alkenyl, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide, halogen, heteroaryl or phenyl; and wherein C_{2-6} alkenyl, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{3-7} cycloalkyl, heteroaryl or phenyl may be optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{2-6} alkenyl, C_{1-6} alkyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl and thiol;

iv) R_{3a} is selected from the group consisting of H, C_{1-6} acyl, C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-8} dialkylamino, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide, C_{2-8} dialkylsulfonamide, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, thiol, nitro and sulfonamide; and

v) R_4 , R_{4a} , R_5 and R_{5a} are independently H, C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-6} alkylureyl, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide, halogen, C_{1-4}

haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, hydroxyl, thiol, 5 or 6 membered-heteroaryl, nitro, phenyl or NR₆R₇, and where the 5 or 6 membered-heteroaryl or phenyl is optionally substituted with a substituents selected from the group consisting of H, C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₆ alkyl, C₁₋₅ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylthio, C₁₋₆ alkylureyl, carbo-C₁₋₆-alkoxy, carboxamide, carboxy, cyano, C₃₋₇ cycloalkyl, C₂₋₈ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, hydroxyl, thiol and nitro;

wherein:

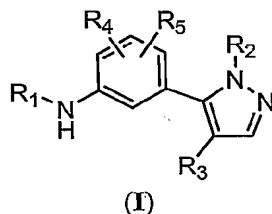
R₆ and R₇ are independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl, phenyl and benzyl group; wherein each said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl, phenyl and benzyl group is optionally substituted with 1 to 5 substituents selected independently from the group consisting of H, C₁₋₅ acyl, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₆ alkyl, C₁₋₅ alkylcarboxamide, C₁₋₄ alkylthio, carbo-C₁₋₆-alkoxy, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, carboxamide, carboxy, cyano, C₃₋₇ cycloalkyl, C₂₋₈ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, hydroxyl, thiol and nitro; or

R₆ and R₇ together with the nitrogen to which they are bonded form a 5, 6 or 7 membered cyclic structure which can be saturated or unsaturated and can contain up to four heteroatoms selected from O, NR₈ or S and said cyclic structure may be optionally substituted with 1 to 5 substituents selected independently from the group consisting of H, C₁₋₅ acyl, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₆ alkyl, C₁₋₅ alkylcarboxamide, C₁₋₄ alkylthio, carbo-C₁₋₆-alkoxy, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, carboxamide, carboxy, cyano, C₃₋₇ cycloalkyl, C₂₋₈ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, hydroxyl, thiol and nitro;

R₈ is H or C₁₋₆ alkyl; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

One aspect of the present invention encompasses certain diarylamine and arylheteroaryl-amine derivatives of Formula (A) wherein R_{3a}, R_{4a}, and R_{5a} are each H and is represented by Formula (I):



or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_1 , R_2 , R_3 , R_4 and R_5 are as defined herein.

Some embodiments of the present invention include pharmaceutical compositions comprising compounds as described herein and a pharmaceutically acceptable carrier.

Some embodiments of the present invention are methods for modulating the activity of a human $5HT_{2A}$ serotonin receptor comprising contacting the receptor with a compound or a pharmaceutical composition as described herein.

Some embodiments of the present invention are methods for the prophylaxis or treatment of reducing platelet aggregation in an individual comprising administering to the individual in need of such prophylaxis or treatment a compound or a pharmaceutical composition as described herein.

Some embodiments of the present invention are methods for the prophylaxis or treatment of an indication selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation in an individual comprising administering to the individual in need of such treatment or prophylaxis a compound or a pharmaceutical composition as described herein.

Some embodiments of the present invention are methods for the prophylaxis or treatment of reducing a risk of blood clot formation in an angioplasty or coronary bypass surgery individual, comprising administering to the individual in need of such prophylaxis or treatment a compound or a pharmaceutical composition as described herein.

Some embodiments of the present invention are methods for the prophylaxis or treatment of reducing risk of blood clot formation in an individual suffering from atrial fibrillation, comprising administering to the individual in need of such prophylaxis or treatment a compound or a pharmaceutical composition as described herein.

Some embodiments of the present invention are methods for the prophylaxis or treatment of asthma in an individual, comprising administering to the individual in need of such prophylaxis or treatment a compound or a pharmaceutical composition as described herein.

Some embodiments of the present invention are methods for the prophylaxis or treatment of a symptom of asthma in an individual, comprising administering to the

individual in need of such prophylaxis or treatment a compound or a pharmaceutical composition as described herein.

Some embodiments of the present invention are methods for the prophylaxis or treatment of agitation or a symptom thereof in an individual, comprising administering to the individual in need of such prophylaxis or treatment a compound or a pharmaceutical composition as described herein. In some embodiments the individual is a cognitively intact elderly individual.

Some embodiments of the present invention are methods for prophylaxis or treatment of agitation or a symptom thereof in an individual suffering from dementia, comprising administering to the individual in need of such prophylaxis or treatment a compound or a pharmaceutical composition as described herein. In some embodiments the dementia is due to a degenerative disease of the nervous system. In some embodiments the dementia is Alzheimers disease, Lewy Body, Parkinson's disease, or Huntington's disease. In some embodiments the dementia is due to diseases that affect blood vessels. In some embodiments the dementia is due to stroke or multi-infarct dementia.

Some embodiments of the present invention are methods for the prophylaxis or treatment of an individual suffering from at least one of the indications selected from the group consisting of behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia comprising administering to the individual in need of such prophylaxis or treatment a dopamine D2 receptor antagonist and a compound or a pharmaceutical composition as described herein. In some embodiments the dopamine D2 receptor antagonist is haloperidol.

Some embodiments of the present invention are methods for the prophylaxis or treatment of an individual with infantile autism, Huntington's chorea, or nausea and/or vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the individual in need of such prophylaxis or treatment a dopamine D2 receptor antagonist and a compound or a pharmaceutical composition as described herein. In some embodiments the dopamine D2 receptor antagonist is haloperidol.

Some embodiments of the present invention are methods for the prophylaxis or treatment of schizophrenia in an individual, comprising administering to the individual in need of such prophylaxis or treatment a dopamine D2 receptor antagonist and a compound or a pharmaceutical composition as described herein. In some embodiments the dopamine D2 receptor antagonist is haloperidol.

Some embodiments of the present invention are methods for the prophylaxis or treatment of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to an individual suffering from schizophrenia, comprising administering to the individual in need of such prophylaxis or treatment a compound or a pharmaceutical composition as described herein.

Some embodiments of the present invention include methods for the prophylaxis or treatment wherein haloperidol and the compound or pharmaceutical composition are administered in separate dosage forms.

Some embodiments of the present invention include methods for the prophylaxis or treatment wherein haloperidol and said compound or pharmaceutical composition are administered in a single dosage form.

Some embodiments of the present invention include methods for the prophylaxis or treatment of a sleep disorder in an individual comprising administering to said individual in need of such prophylaxis or treatment a compound or a pharmaceutical composition as described herein.

Some embodiments of the present invention are compounds described herein for use in a method of treatment of the human or animal body by therapy.

Some embodiments of the present invention are compounds described herein for use in a method for the prophylaxis or treatment of reducing platelet aggregation in the human or animal body by therapy.

Some embodiments of the present invention are compounds described herein for use in a method for the prophylaxis or treatment of an indication selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation in the human or animal body by therapy.

Some embodiments of the present invention are compounds described herein for use in a method for the prophylaxis or treatment of reducing risk of blood clot formation in an angioplasty or coronary bypass surgery in the human or animal body by therapy.

Some embodiments of the present invention are compounds described herein for use in a method for the prophylaxis or treatment of reducing risk of blood clot formation in the human or animal body by therapy.

Some embodiments of the present invention are compounds described herein for use in a method for the prophylaxis or treatment of asthma in the human or animal body by therapy.

Some embodiments of the present invention are compounds described herein for use in a method for the prophylaxis or treatment of a symptom of asthma in the human or animal body by therapy.

Some embodiments of the present invention are compounds described herein for use in a method for the prophylaxis or treatment of agitation or a symptom thereof in the human or animal body by therapy.

Some embodiments of the present invention are compounds described herein for use in a method for the prophylaxis or treatment of at least one of the indications selected from the group consisting of behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia in the human or animal body by therapy.

Some embodiments of the present invention are compounds described herein for use in a method for the prophylaxis or treatment of a sleep disorder in the human or animal body by therapy.

One aspect of the present invention pertains to the use of a compound, as described herein, for the manufacture of a medicament for use in the treatment of a 5HT_{2A} mediated disorder.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the disorder is platelet aggregation.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the disorder is selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the disorder is a blood clot formation in an angioplasty or coronary bypass surgery individual.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the disorder is a blood clot formation in an individual suffering from atrial fibrillation.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the disorder is asthma.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the disorder is a symptom of asthma.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the disorder is agitation or a symptom thereof in an individual. In some embodiments the individual is a cognitively intact elderly individual.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the disorder is agitation or a symptom thereof in an individual suffering from dementia. In some embodiments the dementia is due to a degenerative disease of the nervous system. In some embodiment the dementia is Alzheimers disease, Lewy Body, Parkinson's disease, or Huntington's disease. In some embodiments the dementia is due to diseases that affect blood vessels. In some embodiments the dementia is due to stroke or multi-infract dementia.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder further comprising a dopamine D2 receptor antagonist wherein the disorder is selected from the group consisting of a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia. In some embodiments the dopamine D2 receptor antagonist is haloperidol.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder further comprising a dopamine D2 receptor antagonist wherein the disorder is infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies. In some embodiments the dopamine D2 receptor antagonist is haloperidol.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated

disorder further comprising a dopamine D2 receptor antagonist wherein the disorder is schizophrenia. In some embodiments the dopamine D2 receptor antagonist is haloperidol.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the disorder is a negative symptom or symptoms of schizophrenia induced by the administration of haloperidol.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the haloperidol and the compound or pharmaceutical composition are administered in separate dosage forms.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a 5HT_{2A} mediated disorder wherein the haloperidol and the compound or pharmaceutical composition are administered in a single dosage form.

One embodiment of the present invention pertains to the use of a compound for the production of a medicament for use in the prophylaxis or treatment of a sleep disorder.

One aspect of the present invention is a process for preparing a composition comprising admixing a compound, as described herein, and a pharmaceutically acceptable carrier.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

DETAILED DESCRIPTION

The present invention provides compounds that are useful, for example, for the prophylaxis or treatment of 5HT_{2A} related disorders. The present invention may be understood more readily by reference to the following detailed description of the invention and the Examples included therein and to the Figures and their previous and following description. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

DEFINITIONS

In the specification and Formulae described herein the following terms are hereby defined.

AGONISTS shall mean moieties that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

AMINO ACID ABBREVIATIONS used herein are set out in TABLE 1:

TABLE 1		
ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I
LEUCINE	LEU	L
LYSINE	LYS	K
METHIONINE	MET	M
PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRP	W
TYROSINE	TYR	Y
VALINE	VAL	V

PARTIAL AGONISTS shall mean moieties which activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists.

ANTAGONIST shall mean moieties that competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. **ANTAGONISTS** do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

CHEMICAL GROUP, MOIETY OR RADICAL:

A **chemical group, moiety or radical** of a compound of the present invention, as used in the specification and concluding claims, refers to a structural fragment of the compound.

The term "**C₁₋₅ acyl**" denotes an alkyl radical bonded directly to a carbonyl group [i.e., -C(O)-] wherein the definition of alkyl has the same definition as

described herein; some examples include formyl, acetyl, propionyl, butanoyl, *iso*-butanoyl, pentanoyl, and the like.

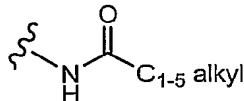
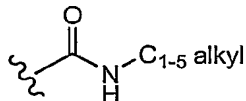
The term "**C₁₋₅ acyloxy**" denotes an acyl radical attached to an oxygen atom wherein acyl has the same definition as described herein; some examples include acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy and the like.

The term "**C₂₋₆ alkenyl**" denotes a radical containing 2 to 6 carbons wherein at least one carbon-carbon double bond is present, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Both *E* and *Z* isomers are embraced by the term "**alkenyl**." Furthermore, the term "**alkenyl**" includes di- and tri-alkenyls. Accordingly, if more than one double bond is present then the bonds may be all *E* or *Z* or a mixtures of *E* and *Z*. Examples of an alkenyl include vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl and the like.

The term "**C₁₋₄ alkoxy**" as used herein denotes a radical alkyl, as defined herein, attached directly to an oxygen atom. In some embodiments, the alkoxy group contains 1 to 3 carbons (i.e., C₁₋₃ alkoxy). Examples of an alkoxy group include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy and the like.

The term "**C₁₋₆ alkyl**" denotes a straight or branched carbon radical containing 1 to 6 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples of an alkyl include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *t*-butyl, amyl, *t*-amyl, *n*-pentyl, *n*-hexyl and the like.

The term "**C₁₋₅ alkylcarboxamido**" denotes a single alkyl group attached to either the nitrogen or carbonyl of an amide group, wherein alkyl has the same definition as found herein. The C₁₋₅ alkylcarboxamido may be represented by the following formulae:



Examples include *N*-methylcarboxamide, *N*-ethylcarboxamide, *N*-(*iso*-propyl)carboxamide and the like.

The term "**C₁₋₄ alkylsulfinyl**" denotes an alkyl radical attached to a sulfoxide radical of the formula: $-S(O)-$ wherein the alkyl radical has the same definition as described herein. Examples include methylsulfinyl, ethylsulfinyl and the like.

The term "**C₁₋₄ alkylsulfonamide**" denotes an alkyl radical attached to the nitrogen or sulfur of a sulfonamide group of the formula: $-S(O)_2NH-$ wherein the alkyl radical has the same definition as described herein and a **C₁₋₄ alkylsulfon-amide** may be represented by the following formulae:



The term "**C₁₋₄ alkylsulfonyl**" denotes an alkyl radical attached to a sulfone radical of the formula: $-S(O)_2-$ wherein the alkyl radical has the same definition as described herein. Examples include methylsulfonyl, ethylsulfonyl and the like.

The term "**C₁₋₄ alkylthio**" denotes an alkyl radical attached to a sulfide group of the formula: $-S-$ wherein the alkyl radical has the same definition as described herein. Examples include methylsulfide (i.e., CH_3S-), ethylsulfide, isopropylsulfide and the like.

The term "**C₁₋₆ alkylureyl**" denotes the group of the formula: $-NC(O)N-$ wherein one or both of the nitrogens are substituted with the same or different alkyl group wherein alkyl has the same definition as described herein. Examples of an alkylureyl include, $CH_3NHC(O)NH-$, $NH_2C(O)NCH_3-$, $(CH_3)_2N(O)NH-$, $(CH_3)_2N(O)NH-$, $(CH_3)_2N(O)NCH_3-$, $CH_3CH_2NHC(O)NH-$, $CH_3CH_2NHC(O)NCH_3-$, and the like.

The term "**C₂₋₆ alkynyl**" denotes a radical containing 2 to 6 carbons and at least one carbon-carbon triple bond, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Examples of an alkynyl include ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 4-hexyne, 5-hexyne and the like. The term "**alkynyl**" includes di- and tri-ynes.

The term "**amino**" denotes the group $-NH_2$.

The term "**C₁₋₄ alkylamino**" denotes one alkyl radical attached to an amino radical wherein the alkyl radical has the same meaning as described herein. Some examples include methylamino, ethylamino, propylamino and the like.

The term "**aryl**" denotes an aromatic ring radical containing 6 to 10 ring carbons. Some examples include phenyl, naphthyl and the like.

The term “**arylalkyl**” defines a C₁-C₄ alkylene, such as -CH₂-, -CH₂CH₂- and the like, which is further substituted with an aryl group. Examples of an “arylalkyl” include benzyl, phenethylene and the like.

The term “**arylcarboxamido**” denotes a single aryl group attached to the amine of an amide, wherein aryl has the same definition as found herein. The example is *N*-phenylcarboxamide.

The term “**arylureyl**” denotes the group -NC(O)N- where one of the nitrogens are substituted with an aryl.

The term “**benzyl**” denotes the group -CH₂C₆H₅.

The term “**carbo-C₁₋₆-alkoxy**” refers to an alkyl ester of a carboxylic acid, wherein the alkyl group is C₁₋₆. Examples include carbomethoxy, carboethoxy, carboisopropoxy and the like.

The term “**carboxamide**” denotes the group -CONH₂.

The term “**carboxy**” or “**carboxyl**” denotes the group -CO₂H; also referred to as a carboxylic acid.

The term “**cyano**” denotes the group -CN.

The term “**C₃₋₇ cycloalkyl**” denotes a saturated ring radical containing 3 to 7 carbons; some embodiments contain 3 to 6 carbons; some embodiments contain 3 to 5 carbons, some embodiments contain 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term “**C₂₋₆ dialkylamino**” denotes an amino substituted with two of the same or different alkyl radicals wherein alkyl radical has the same definition as described herein. Some examples include dimethylamino, methylethylamino, diethylamino and the like.

The term “**C₂₋₈ dialkylcarboxamide**” denotes two alkyl radicals, that are the same or different, attached to an amide group, wherein alkyl has the same definition as described herein. A C₂₋₈ dialkylcarboxamide may be represented by the following groups:



Examples of a dialkylcarboxamide include *N,N*-dimethylcarboxamide, *N*-methyl-*N*-ethylcarboxamide and the like.

The term "**C₂₋₈ dialkylsulfonamide**" denotes two alkyl radicals attached independently to the nitrogen or sulfur of a sulfonamide group of the formula: $S(O)_2N$ wherein the alkyl radicals have the same definition as described herein and may be the same or different; a **C₂₋₈ alkylsulfonamide** may be represented by the following formulae:



The term "**halo**" or "**halogen**" denotes to a fluoro, chloro, bromo or iodo atom.

The term "**C₁₋₄ haloalkoxy**" denotes a haloalkyl, as defined herein, that is directly attached to an oxygen to form a difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and the like.

The term "**C₁₋₄ haloalkyl**" denotes an alkyl group, defined herein, wherein the alkyl is substituted with one halogen up to completely substituted with halogens and may be represented by the formula $C_n\text{Halogen}_{2n+1}$; when more than one halogen is present they may be the same or different and selected from F, Cl, Br or I. In some embodiments, the haloalkyl contains 1 to 3 carbons (i.e., **C₁₋₃ haloalkyl**). Examples of an haloalkyl group include fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, bromodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

The term "**C₁₋₄ haloalkylsulfinyl**" denotes a haloalkyl radical attached to a sulfoxide of the formula: $-S(O)-$ wherein the alkyl radical has the same definition as described herein. Examples include trifluoromethylsulfinyl, chlorodifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

The term "**C₁₋₄ haloalkylsulfonyl**" denotes a haloalkyl radical attached to a sulfone of the formula: $-S(O)_2-$ wherein haloalkyl has the same definition as described herein. Examples include trifluoromethylsulfonyl, chlorodifluoro-methylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.

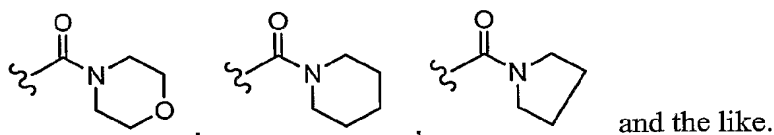
The term "**C₁₋₄ haloalkylthio**" denotes an alkylthio radical substituted with one or more halogens. Examples include trifluoromethylthio, 1,1-difluoroethylthio, 2,2,2-trifluoroethylthio and the like.

The term "**heteroaryl**" denotes an aromatic ring system that may be a single ring, such as 5 or 6-membered ring containing carbons and at least one ring heteroatom selected from O, S and N or a heteroaryl group may be a 5 or 6-membered ring fused

with a phenyl or another heteroaryl ring system. Examples of heteroaryl groups include, but not limited to, quinolinyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, quinazolinyl, pyrimidinyl, pyridyl, pyrazinyl, pyridazinyl, triazinyl, isoquinolinyl, quinazolinyl, quinoxalyl and the like.

The term “**heterocyclic**” denotes a 5, 6 or 7 membered non-aromatic carbon ring wherein at least one ring carbon is replaced by one, two or three heteroatoms, such as, piperidinyl, morpholinyl, piperziny, pyrrolidinyl, and the like.

The term “**heterocycliccarboxamido**” denotes a heterocyclic group with a ring nitrogen where the ring nitrogen is bonded directly to the carbonyl forming an amide. Examples include:



The term “**hydroxyl**” refers to the group -OH.

The term “**nitro**” refers to the group -NO₂.

The term “**perfluoroalkyl**” denotes the group of the formula -C_nF_{2n+1}; stated differently, a perfluoroalkyl is an alkyl as defined herein wherein the alkyl is fully substituted with fluorine atoms and is therefore considered a subset of haloalkyl.

Examples of perfluoroalkyls include CF₃, CF₂CF₃, CF₂CF₂CF₃, CF(CF₃)₂, CF₂CF₂CF₂CF₃, CF₂CF(CF₃)₂, CF(CF₃)CF₂CF₃ and the like.

The term “**phenoxy**” refers to the group C₆H₅O-.

The term “**phenyl**” refers to the group C₆H₅-.

The term “**thiol**” denotes the group -SH.

COMPOSITION shall mean a material comprising at least two compounds or two components; for example, and not limitation, a Pharmaceutical Composition is a Composition.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity.

CONTACT or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

INDIVIDUAL as used herein refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

INHIBIT or **INHIBITING**, in relationship to the term “response” shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

IN NEED OF PROPHYLAXIS OR TREATMENT as used herein refers to a judgement made by a caregiver (e.g. physician, nurse, nurse practitioner, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual requires or will benefit from prophylaxis or treatment. This judgement is made based on a variety of factors that are in the realm of a caregiver’s expertise, but that includes the knowledge that the individual or animal is ill, or will be ill, as the result of a condition that is treatable by the compounds of the invention.

INVERSE AGONISTS shall mean moieties that bind the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

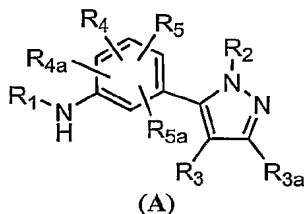
As used herein, the terms **MODULATE** or **MODULATING** shall mean to refer to an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule. For example, Compounds which modulate/capable of modulating the 5HT_{2A} activity include agonists, inverse agonists, antagonists, inhibitors, activators, and compounds which directly or indirectly affect regulation of the 5HT_{2A} activity.

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

STIMULATE or **STIMULATING**, in relationship to the term “response” shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

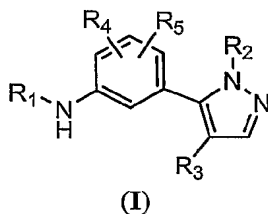
Compound Of The Present Invention

One aspect of the present invention pertains to certain diarylamine and arylheteroaryl-amine derivatives as shown in Formula (A):



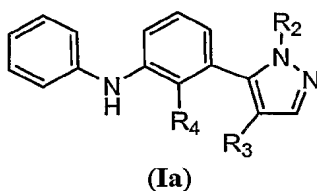
or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_1 , R_2 , R_3 , R_{3a} , R_4 , R_{4a} , R_5 , and R_{5a} are as described herein.

One aspect of the present invention encompasses certain diarylamine and arylheteroaryl-amine derivatives of Formula (A) wherein R_{3a} , R_{4a} , and R_{5a} are each H and is represented by Formula (I):



or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_1 , R_2 , R_3 , R_4 and R_5 are as defined herein.

In some embodiments of the present invention, the compound is not a compound of Formula (Ia):



wherein:

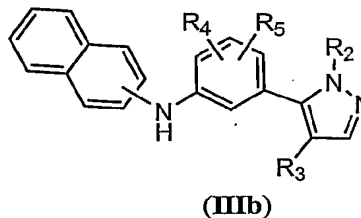
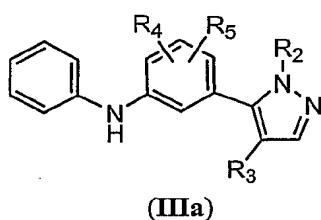
R_2 is C_{1-6} alkyl;

R_3 is: H, or halogen atom, an C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, optionally substituted with halogen, a phenyl optionally substituted with C_{1-3} alkyl, C_{1-3} haloalkyl or C_{1-3} alkoxy, or a carboxy; and

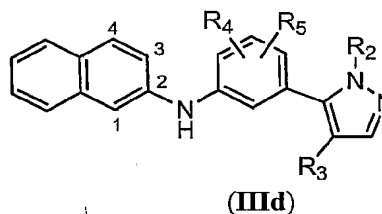
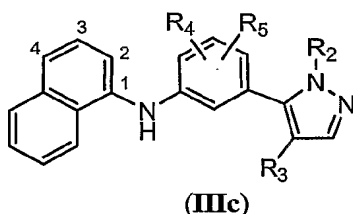
R_4 is H, cyano, halogen atom, hydroxyl, thiol, nitro or NR_6R_7 ; wherein R_6 and R_7 are independently C_{1-6} alkyl or phenyl.

Formula (Ia) explicitly shows the R_1 as a phenyl group that is substituted with only hydrogens atoms.

In some embodiments, compounds of the present invention are when R_1 is aryl and may be represented by Formulae (IIIa) and (IIIb):



the R_1 phenyl group of Formula (IIIa) and R_1 naphthyl group of Formula (IIIb) may be optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, carboxy, carbo- C_{1-6} -alkoxy, cyano, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, thiol, nitro and phenoxy. In some embodiments the C_{1-6} alkyl substituents is optionally substituted with 1 to 3 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-5} alkylcarboxamide, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl and thiol. It is understood that in some embodiments, R_1 is naphth-1-yl, Formula (IIIc), and naphth-2-yl, Formula (IIId), accordingly, both aryl groups are embraced in Formula (IIIb).



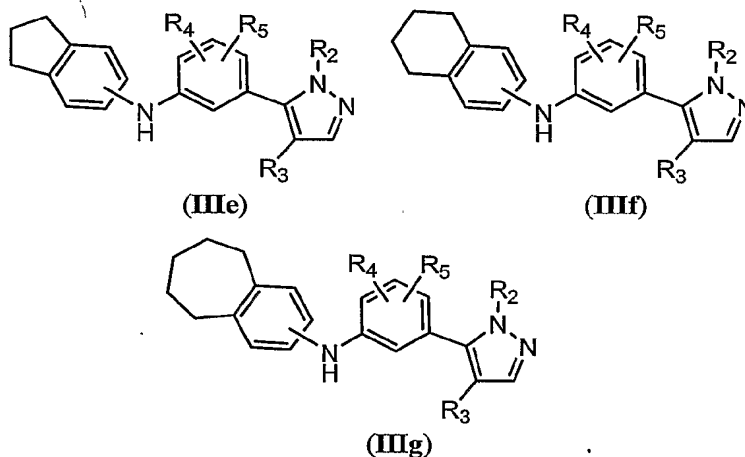
In some embodiments R_1 is aryl, such as phenyl [Formula (IIIa)] or naphthyl [Formula (IIIb)], and optionally substituted with 1 to 5 substituents selected independently from the group consisting of NO_2 , F, Cl, Br, I, CF_3 , CF_2CF_3 , OCH_3 , OCH_2CH_3 , OCF_3 , OCF_2CF_3 , SCH_3 , SCH_2CH_3 , $S(O)CH_3$, $S(O)CH_2CH_3$, $S(O)_2CH_3$, $S(O)_2CH_2CH_3$, CO_2H , CN, $COCH_3$, $COCH_2CH_3$, CH_3 , CH_2CH_3 , $NHCOCH_3$, CH_2OH and OC_6H_5 . In some embodiments R_1 is aryl, such as phenyl [Formula (IIIa)] or naphthyl [Formula (IIIb)], and optionally substituted with 1 to 3 substituents selected independently from the group consisting of NO_2 , F, Cl, Br, I, CF_3 , OCH_3 , OCF_3 , SCH_3 , $S(O)CH_3$, $S(O)_2CH_3$, CN, $COCH_3$, CH_3 , CH_2OH and OC_6H_5 . In some embodiments R_1 is aryl, such as phenyl [Formula (IIIa)] or naphthyl [Formula (IIIb)], and optionally substituted with 1 to 3 substituents selected independently from the group consisting of NO_2 , F, Cl, Br, I, CF_3 , OCH_3 , OCF_3 , SCH_3 , $S(O)CH_3$, $S(O)_2CH_3$, CN and CH_3 . In some embodiments of the invention R_1 is aryl, such as phenyl [Formula

(IIIa)] or naphthyl [Formula (IIIb)], and optionally substituted with 1 to 3 substituents selected independently from the group consisting of F, Cl, Br, I, CF₃, OCH₃ and OCF₃.

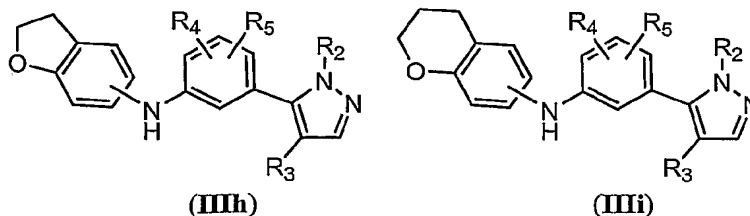
In some embodiments, compounds of the present invention are when aryl is phenyl, as represented herein as [Formula (IIIa)], and optionally substituted with 1 to 3 substituents selected independently from the group consisting of F, Cl, Br, I, CF₃, OCH₃ and OCF₃.

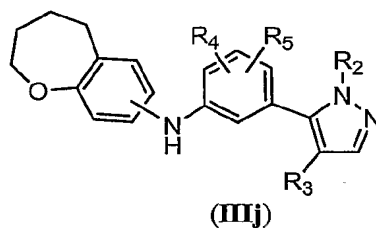
In some embodiments, compounds of the present invention are when aryl is 2-naphthyl, as represented in [Formula (IIId)], and optionally substituted with 1 to 3 substituents selected independently from the group consisting of F, Cl, Br, I, CF₃, OCH₃ and OCF₃.

In some embodiments, compounds of the present invention are when R₁ is aryl and two adjacent substituents together with the ring carbons to which they are bonded form a C₅₋₇ cycloalkyl optionally replaced with 1 to 2 oxygen atoms. In some embodiments the C₅₋₇ cycloalkyl together with the aryl may be represented by Formulae (IIIe)-(IIIg):

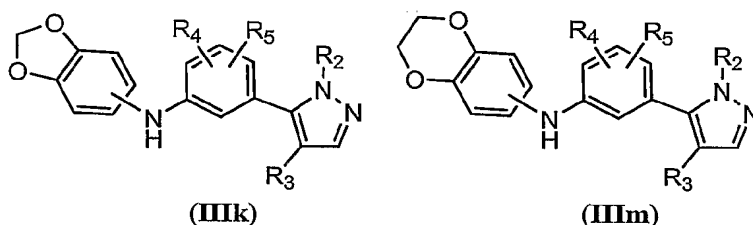


In some embodiments, the C₅₋₇ cycloalkyl is replaced with 1 to 2 oxygen atoms, accordingly, 1 or 2 cycloalkyl ring carbons is replaced with an oxygen atom. In some embodiments, 1 oxygen atom is present as shown in Formula (IIIh)-(IIIj):





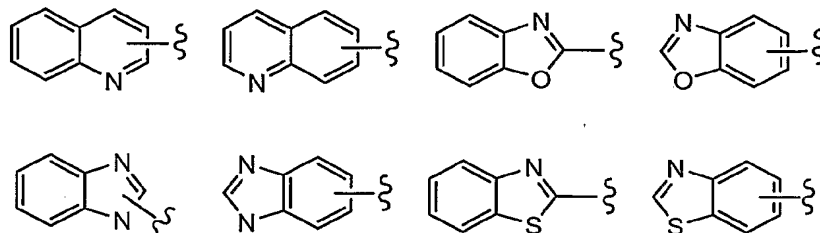
In some embodiments, 2 oxygen atoms are present in the ring. In some embodiments, R_1 is a 3,4-methylenedioxyphenyl or 3,4-ethylenedioxyphenyl group represented by Formula (IIIk) and (IIIm).



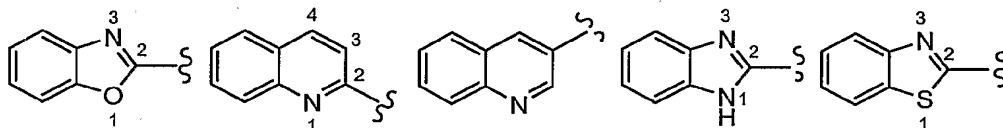
In some embodiments, compounds of Formulae (IIIe)-(IIIm) are optionally substituted with 1 to 3 substituents selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, carboxy, carbo- C_{1-6} -alkoxy, cyano, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, thiol, nitro and phenoxy; and where C_{1-6} alkyl is optionally substituted with 1 to 3 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-5} alkylcarboxamide, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl and thiol.

In some embodiments, compounds of the present invention are when R_1 is heteroaryl and is optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, carboxy, carbo- C_{1-6} -alkoxy, cyano, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, thiol, nitro and phenoxy; and where C_{1-6} alkyl is optionally substituted with 1 to 3 substituents selected from the group consisting of C_{1-4} alkoxy, C_{1-5} alkylcarboxamide, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl and thiol. In some embodiments R_1 is heteroaryl and is optionally substituted with 1 to 3 substituents selected independently from the group consisting of C_{1-4} alkoxy, C_{1-6} alkyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, thiol and nitro.

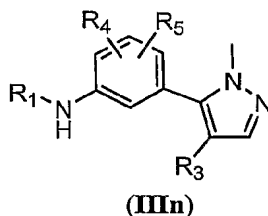
In some embodiments the heteroaryl is selected from the group consisting of quinolinyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, quinazoliny and pyrimidinyl as represented below:



In some embodiments the heteroaryl is selected from the group consisting of benzoxazol-2-yl, quinolin-2-yl, quinolin-3-yl benzimidazol-2-yl, and benzothiazol-2-yl as represented below:



In some embodiments, compounds of the present invention are when R_2 is C_{1-6} alkyl. In some embodiments R_2 is CH_3 , CH_2CH_3 , $CH(CH_3)_2$, or $CH_2CH_2CH_3$. In some embodiments R_2 is CH_3 and is represented by Formula (III_n):



In some embodiments, compounds of the present invention are when R_3 is H, C_{2-6} alkenyl, C_{1-6} alkyl, C_{2-6} alkynyl, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, halogen, 5 membered-heteroaryl or phenyl; and where C_{2-6} alkenyl, C_{1-6} alkyl or phenyl group may be optionally substituted with 1 to 3 substituents selected independently from the group consisting of C_{1-4} alkoxy, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy and hydroxyl. In some embodiments R_3 is H, Cl, Br, CO_2CH_3 , $CO_2CH_2CH_3$, 2-hydroxyethyl, 2-dimethylaminoethyl, 2-diethylaminoethyl, vinyl, CH_3 , CH_2CH_3 , phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, CO_2H , cyclopropyl, $-C\equiv CH$, $-CH=CH-C\equiv CH$ or CN. In some embodiments R_3 is H, Cl or Br.

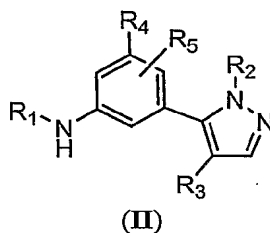
Some embodiments of the present invention are compounds of Formula (I) wherein R_{3a} is selected from the group consisting of H, C_{1-6} alkyl and C_{1-6} haloalkyl.

In some embodiments, R_{3a} is selected from the group consisting of H, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CFH}_2$, $-\text{CF}_2\text{CF}_3$ and $-\text{CH}_2\text{CF}_3$. In some embodiments, R_{3a} is H or $-\text{CF}_3$. In some embodiments, R_{3a} is H.

In some embodiments R_4 is H, halogen or NR_6R_7 , wherein R_6R_7 is as defined herein. In some embodiments, R_4 is H, F, $\text{N}(\text{CH}_3)_2$, or pyrrolidin-1-yl. In some embodiments, R_4 is H.

In some embodiments, R_5 is halogen, or H. In some embodiments, R_5 is H.

In some embodiments, compounds of the present invention are represented by Formula (II):



wherein:

R_1 , R_2 and R_3 have the same meaning as described herein;

R_4 is H, C_{1-4} alkoxy, phenyl, halogen, 5 or 6 membered-heteroaryl, hydroxyl, thiol or NR_6R_7 , where the phenyl or heteroaryl group is optionally substituted with 1 to 5 substituents independently selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, cyano, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, thiol and nitro; and

wherein:

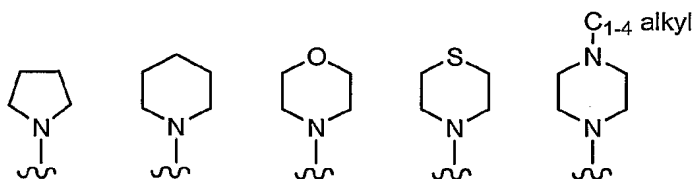
R_6 and R_7 are independently H, C_{1-6} alkyl, or

R_6 and R_7 together with the nitrogen to which they are bonded form a 5, 6 or 7 membered cyclic structure that may contain up to four heteroatoms selected from O, S or N- C_{1-4} alkyl; and

R_5 is H, C_{1-4} alkoxy, C_{1-6} alkyl, carboxamide, carboxy, cyano, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, thiol or nitro.

In some embodiments R_4 is NR_6R_7 wherein R_6 and R_7 together with the nitrogen to which they are bonded form a 5, 6 or 7 membered cyclic structure and may contain up to four

heteroatoms selected from O, S or N-C₁₋₄ alkyl; these groups may be represented by the following Formulae:

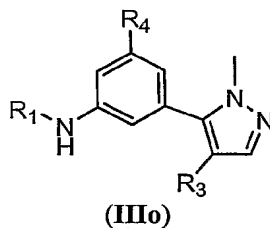


In some embodiments, compounds of the present invention are when R₄ is H, Cl, F, dimethylamino, diethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, hydroxyl, thiol, OCH₃ or OCH₂CH₃. In some embodiments R₅ is H or halogen.

In some embodiments, compounds of the present invention are when R₂ is CH₃. In some embodiments R₃ is H, Cl or Br.

In some embodiments R₄ is H, Cl, F, N(CH₃)₂ also referred to as dimethylamino, diethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, hydroxyl, thiol, OCH₃ or OCH₂CH₃.

One embodiment of the present invention includes compounds of Formula (IIIo):



wherein:

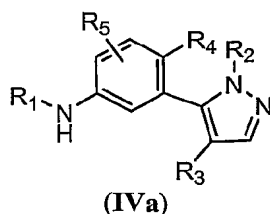
R₁ is phenyl substituted with 1 to 3 substituents selected independently from the group consisting of F, Cl, Br, I, CF₃, OCH₃ and OCF₃;

R₃ is H, Cl or Br; and

R₄ is H, Cl, F, dimethylamino, diethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, hydroxyl, thiol, OCH₃ or OCH₂CH₃; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

In some embodiments, compounds of the present invention are represented by Formula (IVa):



wherein R_1 , R_2 , R_3 , R_4 and R_5 have the same meaning as described above.

In some embodiments, compounds have the Formula (IVa) wherein R_4 is H, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{1-4} alkylsulfonamide, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, 5 or 6 membered-heteroaryl, phenyl or NR_6R_7 , and wherein C_{1-6} alkyl, 5 or 6 membered-heteroaryl or phenyl is optionally substituted with a substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-6} alkylureyl, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, thiol and nitro;

wherein: R_6 and R_7 are independently C_{1-6} alkyl optionally substituted with each R_6 and R_7 group may be optionally substituted with 1 to 5 substituents selected independently from the group consisting of H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{1-4} alkylthio, carbo- C_{1-6} -alkoxy, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, carboxamide, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl, thiol and nitro; or

R_6 and R_7 together with the nitrogen to which they are bonded form a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, NR_8 or S and the cyclic structure may be optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, carbo- C_{1-6} -alkoxy, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, carboxy, cyano, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, thiol and nitro; and R_8 is H or C_{1-6} alkyl.

In some embodiments, compounds have the Formula (IVa) wherein R_4 is H, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{1-4} alkylsulfonamide, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl or NR_6R_7 , and wherein C_{1-6} alkyl is optionally substituted with a substituents selected from the group consisting of C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-5}

alkylcarboxamide, C₁₋₄ alkylsulfonamide, carbo-C₁₋₆-alkoxy, carboxamide, carboxy, C₂₋₈ dialkylcarboxamide, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, hydroxyl, thiol and nitro;

wherein R₆ and R₇ are independently C₁₋₆ alkyl; or R₆ and R₇ together with the nitrogen to which they are bonded form a 5, 6 or 7 membered cyclic structure which is saturated and may contain up to four heteroatoms selected from O, NR₈ or S.

In some embodiments, compounds have the Formula (IVa) wherein R₄ is C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, hydroxyl or NR₆R₇; wherein R₆ and R₇ are independently C₁₋₆ alkyl; or R₆ and R₇ together with the nitrogen to which they are bonded form a 5, 6 or 7 membered cyclic structure which is saturated and may contain one heteroatoms selected from O, NR₈ or S, where R₈ is CH₃ or CH₂CH₃.

In some embodiments, compounds have the Formula (IVa) wherein R₄ is OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₂CH₃, OCH(CH₃)CH₂CH₃, OC(CH₃)₂CH₃ or OCH₂CH(CH₃)₂; R₁ is phenyl optionally substituted with 1 to 3 substituents selected independently from the group consisting of NO₂, F, Cl, Br, I, CF₃, OCH₃, OCF₃, SCH₃, S(O)CH₃, S(O)₂CH₃, CN, COCH₃, CH₃, CH₂OH and OC₆H₅; R₂ is C₁₋₆ alkyl and R₃ is H, Cl or Br. In some embodiments, R₁ is phenyl optionally substituted with 1 to 3 substituents selected independently from the group consisting of F, Cl, Br, I, CF₃, OCH₃ and OCF₃. In some embodiments, R₂ is CH₃ or CH₂CH₃. In some embodiments, R₂ is CH₃. In some embodiments, R₃ is Br.

In some embodiments, compounds have the Formula (IVa) wherein R₄ is OCH₃.

In some embodiments, compounds have the Formula (IVa) wherein R₄ is OCF₃, OCHF₂ or OCH₂CF₃; R₁ is phenyl optionally substituted with 1 to 3 substituents selected independently from the group consisting of NO₂, F, Cl, Br, I, CF₃, OCH₃, OCF₃, SCH₃, S(O)CH₃, S(O)₂CH₃, CN, COCH₃, CH₃, CH₂OH and OC₆H₅; R₂ is C₁₋₆ alkyl and R₃ is H, Cl or Br. In some embodiments, R₁ is phenyl optionally substituted with 1 to 3 substituents selected independently from the group consisting of F, Cl, Br, I, CF₃, OCH₃ and OCF₃. In some embodiments, R₂ is CH₃ or CH₂CH₃. In some embodiments, R₂ is CH₃. In some embodiments, R₃ is Br.

In some embodiments, compounds have the Formula (IVa) wherein R₄ is OCF₃.

One embodiment of the present invention is the group of compounds wherein R₁ is phenyl substituted with at least one substituent selected from the group consisting of F, Cl, Br, I, CF₃, OCH₃ and OCF₃; R₂ is CH₃; and R₃, R₄ and R₅ are H.

One embodiment of the present invention is the group of compounds wherein R₁ is a phenyl substituted with at least one substituent selected from the group consisting of F, Cl, Br, I, CF₃, OCH₃ and OCF₃; R₂ is CH₃; R₂ is CH₃; R₂ is Cl; and both R₄ and R₅ are H.

One embodiment of the present invention is the group of compounds wherein R_1 is a phenyl substituted with at least one substituent selected from the group consisting of F, Cl, Br, I, CH_3 , CF_3 , OCH_3 and OCF_3 ; R_2 is CH_3 ; R_2 is CH_3 ; R_2 is Cl; and both R_4 and R_5 are H.

One embodiment of the present invention is the group of compounds wherein R_1 is a phenyl substituted with at least one substituent selected from the group consisting of F, Cl, Br, I, CH_3 , CF_3 , NO_2 , $C(O)CH_3$, $NHC(O)CH_3$, $CHOH$, OC_6H_5 , SCH_3 , $S(O)_2CH_3$, CN, OCH_3 and OCF_3 ; R_2 is CH_3 ; R_2 is CH_3 ; R_2 is Br; and both R_4 and R_5 are H.

One embodiment of the present invention is the group of compounds wherein R_1 is a phenyl substituted with at least one substituent selected from the group consisting of F, Cl, Br, I, CH_3 , CF_3 , NO_2 , $C(O)CH_3$, $NHC(O)CH_3$, $CHOH$, OC_6H_5 , SCH_3 , $S(O)_2CH_3$, CN, OCH_3 and OCF_3 ; or two substituents together with the phenyl form a methylenedioxy group (i.e., - OCH_2O -); R_2 is CH_3 ; R_2 is CH_3 ; R_2 is Br; and both R_4 and R_5 are H.

One embodiment of the present invention is the group of compounds wherein R_1 is a phenyl substituted with at least one substituent selected from the group consisting of F, Cl, CH_3 , CF_3 , CN, OCH_3 and OCF_3 ; R_2 is CH_3 ; R_2 is CH_3 ; R_2 is Br; and both R_4 and R_5 are H.

One embodiment of the present invention is the group of compounds wherein R_1 is a naphthyl optionally substituted with 1 to 3 substituents selected from the group consisting of F, Cl, CH_3 , CF_3 , CN, OCH_3 and OCF_3 ; R_2 is CH_3 ; R_2 is CH_3 ; R_2 is Br; and both R_4 and R_5 are H.

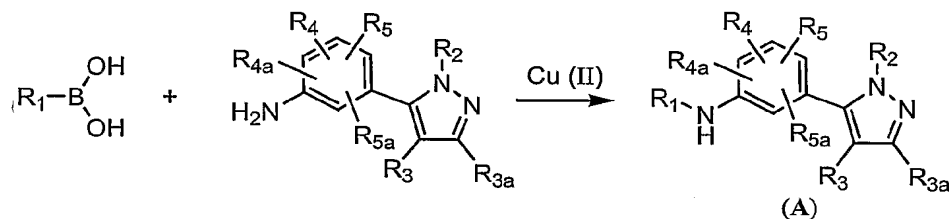
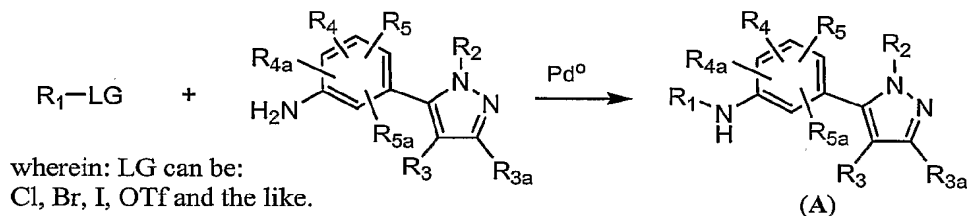
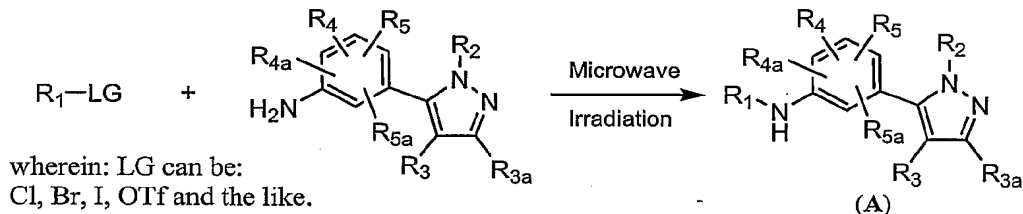
One embodiment of the present invention is the group of compounds wherein R_1 is a heteroaryl selected from benzoxazol-2-yl, quinolin-2-yl, quinolin-3-yl benzimidazol-2-yl, and benzothiazol-2-yl, and each heteroaryl optionally substituted with 1 to 3 substituents selected from the group consisting of F, Cl, CH_3 , CF_3 , CN, OCH_3 and OCF_3 ; R_2 is CH_3 ; R_2 is CH_3 ; R_2 is Br; and both R_4 and R_5 are H.

Some embodiments of the present invention include pharmaceutical compositions comprising compounds described herein and a pharmaceutically acceptable carrier.

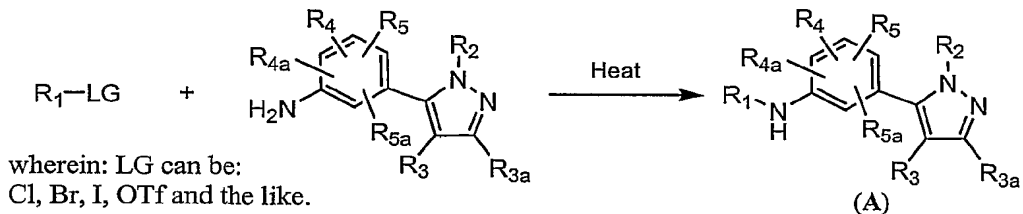
Synthetic Methods for making Compounds of the Invention:

The compounds of the present invention can be readily prepared according to a variety of synthetic regimes, all of which would be familiar to one skilled in the art. The chemical and patent literature quotes general procedures for the synthesis of intermediates and general compounds of Formula (I), one particular reference related to the synthesis of certain R_4 substitutions and to phenyl-pyrazole couplings is U.S. Provisional 60/401,467 filed August 5, 2002 and is incorporated by reference in their entirety.

In the illustrated syntheses outlined below, the labeled substituents have the same identifications as set out in the definitions of the compound described above for Formula (I). The methods described below are useful in the preparation of compounds of the invention. Generally, compounds of Formula (I) were prepared by four separate methods and are labeled Methods A-D.

Method A:**Method B:****Method C:**

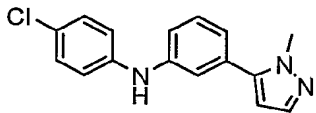
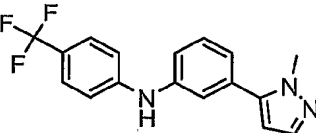
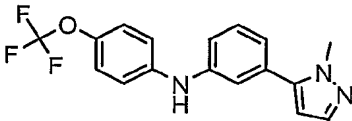
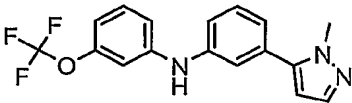
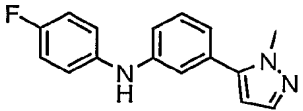
Irradiation with microwaves may be generated from a number of different microwaves sources. One particularly useful instrument in generating microwaves used in organic synthesis is the Smith Synthesizer and related instruments from Personal Chemistry AB, Uppsala Sweden.

Method D:

Additionally, compounds of Formula (I) encompass all pharmaceutically acceptable salts, solvates and particularly hydrates thereof. The present invention also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of Formula (I). Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

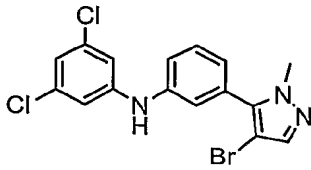
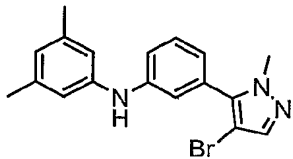
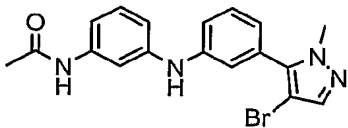
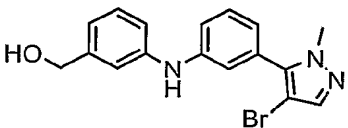
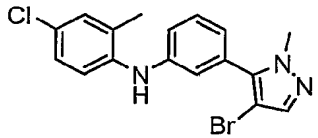
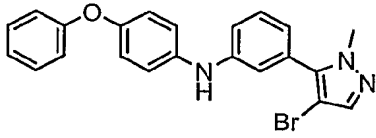
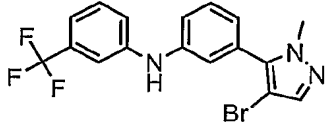
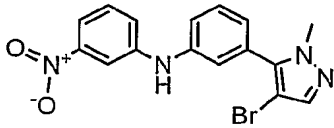
Certain examples of diarylamine and arylheteroarylamine pyrazole derivatives of Formula (I) are shown below in Table 2:

TABLE 2

Compd	Chemical Structure	Chemical Name
1		(4-Chloro-phenyl)-[3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-amine
2		[3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethyl-phenyl)-amine
3		[3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethoxy-phenyl)-amine
4		[3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-(3-trifluoromethoxy-phenyl)-amine
5		[3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-(4-fluoro-phenyl)-amine

Compd	Chemical Structure	Chemical Name
6		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-chloro-phenyl)-amine
7		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethyl-phenyl)-amine
8		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethoxy-phenyl)-amine
9		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-trifluoromethoxy-phenyl)-amine
10		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-fluoro-phenyl)-amine
11		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-methyl-4-chloro-phenyl)-amine
12		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-chloro-4-trifluoromethyl-phenyl)-amine
13		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,4-difluoro-phenyl)-amine

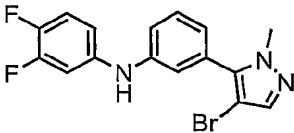
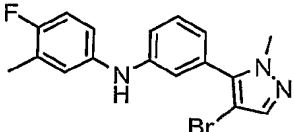
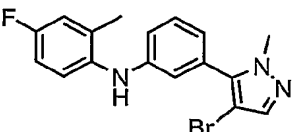
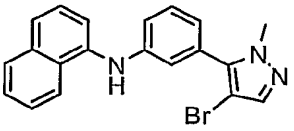
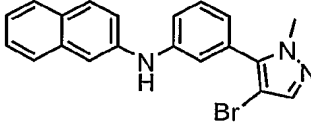
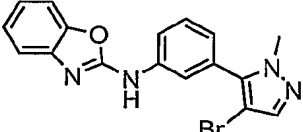
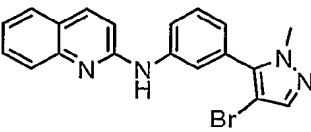
Compd	Chemical Structure	Chemical Name
14		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-chloro-phenyl)-amine
15		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-methoxy-phenyl)-amine
16		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2-nitro-phenyl)-amine
17		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-chloro-phenyl)-amine
18		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,5-bis-trifluoromethyl-phenyl)-amine
19		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-methoxy-phenyl)-amine
20		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,4-dimethoxy-phenyl)-amine
21		1-{3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamino]-phenyl}-ethanone

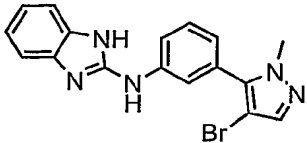
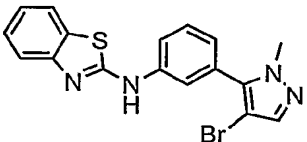
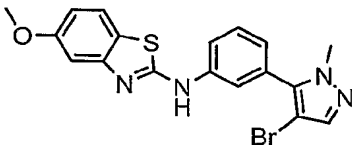
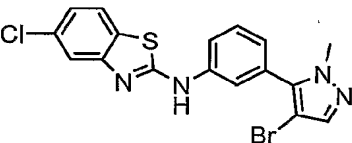
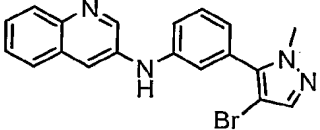
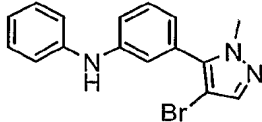
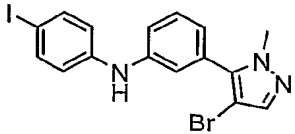
Compd	Chemical Structure	Chemical Name
22		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,5-dichloro-phenyl)-amine
23		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,5-dimethyl-phenyl)-amine
24		<i>N</i> -{3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamino]-phenyl}-acetamide
25		{3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamino]-phenyl}-methanol
26		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2-methyl-4-chloro-phenyl)-amine
27		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-phenoxy-phenyl)-amine
28		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-trifluoromethyl-phenyl)-amine
29		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-nitro-phenyl)-amine

Compd	Chemical Structure	Chemical Name
30		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2,3,4-trimethoxy-phenyl)-amine
31		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-fluoro-4-methyl-phenyl)-amine
32		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2,4-bis-trifluoromethyl-phenyl)-amine
33		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-fluoro-4-methoxy-phenyl)-amine
34		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2,3-difluoro-phenyl)-amine
35		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2,4-difluoro-phenyl)-amine
36		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-chloro-phenyl)-amine

Compd	Chemical Structure	Chemical Name
37		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-fluoro-phenyl)-amine
38		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-methoxy-phenyl)-amine
39		Benzo[1,3]dioxol-5-yl-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-amine
40		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-trifluoromethoxy-phenyl)-amine
41		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-bromo-phenyl)-amine
42		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-methylsulfanyl-phenyl)-amine
43		4-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamino]-benzonitrile
44		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethyl-phenyl)-amine

Compd	Chemical Structure	Chemical Name
45		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethoxy-phenyl)-amine
46		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-methanesulfonyl-phenyl)-amine
47		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-chloro-4-fluoro-phenyl)-amine
48		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,4-dichloro-phenyl)-amine
49		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-methyl-4-chloro-phenyl)-amine
50		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,5-difluoro-phenyl)-amine
51		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-chloro-4-trifluoromethyl-phenyl)-amine

Compd	Chemical Structure	Chemical Name
52		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,4-difluoro-phenyl)-amine
53		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-methyl-4-fluoro-phenyl)-amine
54		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2-methyl-4-fluoro-phenyl)-amine
55		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-naphthalen-1-yl-amine
56		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-naphthalen-2-yl-amine
57		Benzoxazol-2-yl-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-amine
58		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-quinolin-2-yl-amine

Compd	Chemical Structure	Chemical Name
59		(1H-Benzimidazol-2-yl)-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-amine
60		Benzothiazol-2-yl-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-amine
61		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(5-methoxy-benzothiazol-2-yl)-amine
62		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(5-chloro-benzothiazol-2-yl)-amine
63		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-quinolin-3-yl-amine
64		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-phenyl-amine
65		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-iodo-phenyl)-amine

Compd	Chemical Structure	Chemical Name
66		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2-methoxy-5-methyl-phenyl)-amine
67		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(<i>N,N</i> -dimethylamino)-phenyl]-(4-chloro-phenyl)-amine
68		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-(4-chloro-phenyl)-amine
69		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-(4-chloro-phenyl)-amine
70		[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenyl]-(4-chloro-phenyl)-amine
71		(4-Chloro-phenyl)-[4-methoxy-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-amine
72		(4-Chloro-phenyl)-[3-(2-isopropyl-2H-pyrazol-3-yl)-phenyl]-amine

Compd	Chemical Structure	Chemical Name
73		[3-(4-Bromo-2-isopropyl-2H-pyrazol-3-yl)-phenyl]-(4-fluoro-phenyl)-amine
74		[3-(4-Bromo-2-isopropyl-2H-pyrazol-3-yl)-phenyl]-(4-chloro-phenyl)-amine
75		(4-Fluoro-phenyl)-[3-(2-isopropyl-2H-pyrazol-3-yl)-phenyl]-amine
76		[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenyl]-(4-chloro-phenyl)-amine
77		(4-Chloro-phenyl)-[3-(4-fluoro-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenyl]-amine
78		(4-Chloro-phenyl)-[3-(4-fluoro-2-methyl-2H-pyrazol-3-yl)-phenyl]-amine

In addition to the foregoing beneficial uses for the modulators of 5HT_{2A} receptor activity disclosed herein, the compounds disclosed herein are useful in the treatment of one or more additional diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include the following:

1. ANTIPLATELET THERAPIES (5HT_{2A} MEDIATED PLATELET AGGREGATION):

Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

In a myocardial infarction (heart attack), the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 minutes), antiplatelets can reduce the damage to the heart.

A transient ischemic attack ("TIA" or "mini-stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation blood clots that cause first or second strokes.

Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrhythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the heart and traveling to the brain (embolism).

5HT_{2A} receptors are expressed on smooth muscle of blood vessels and 5HT secreted by activated platelets causes vasoconstriction as well as activation of additional platelets

during clotting. There is evidence that a 5HT_{2A} inverse agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy. See Satimura, K, et al., Clin Cardiol **2002** Jan. 25 (1):28-32; and Wilson, H.C et al., Thromb Haemost **1991** Sep 2;66(3):355-60.

The 5HT_{2A} inverse agonists disclosed herein provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limitation, the indications described above. Accordingly, in some embodiments, the present invention provides methods for reducing platelet aggregation in an individual in need thereof comprising administering to the individual a composition comprising a 5HT_{2A} inverse agonist disclosed herein. In further embodiments, the present invention provides methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in an individual in need of said treatment, comprising administering to the individual a composition comprising a 5HT_{2A} inverse agonist disclosed herein.

In further embodiments, the present invention provides methods for reducing risk of blood clot formation in a angioplasty or coronary bypass surgery individual, or an individual suffering from atrial fibrillation, comprising administering to the individual a composition comprising a 5HT_{2A} inverse agonist disclosed herein at a time where such risk exists.

2. ASTHMA

It has been suggested that 5-HT (5-hydroxytryptamine) plays a role in the pathophysiology of acute asthma. See Cazzola, M. and Matera, M.G., TiPS, **2000**, 21, 13; and De Bie, J.J. et al., British J. Pharm., **1998**, 124, 857-864. The compounds of the present invention disclosed herein are useful in the treatment of asthma, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating asthma in an individual in need of said treatment, comprising administering to the individual a composition comprising a 5HT_{2A} inverse agonist disclosed herein. In further embodiments, methods are provided for treating a symptom of asthma in an individual in need of said treatment, comprising administering to the individual a composition comprising a 5HT_{2A} inverse agonist disclosed herein.

3. AGITATION

Agitation is a well-recognized behavioral syndrome with a range of symptoms, including hostility, extreme excitement, poor impulse control, tension and uncooperativeness

(See Cohen-Mansfield J, and Billig, N., (1986), Agitated Behaviors in the Elderly. I. A Conceptual Review. J Am Geriatr Soc 34(10): 711-721).

Agitation is a common occurrence in the elderly and often associated with dementia such as those caused by Alzheimer's disease, Lewy Body, Parkinson's, and Huntington's, which are degenerative diseases of the nervous system and by diseases that affect blood vessels, such as stroke, or multi-infarct dementia, which is caused by multiple strokes in the brain can also induce dementia. Alzheimer's disease accounts for approximately 50 to 70% of all dementias (See Koss E, et al., (1997), Assessing patterns of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 11(suppl 2):S45-S50).

An estimated five percent of people aged 65 and older and up to 20 percent of those aged 80 and older are affected by dementia. Of these sufferers, nearly half exhibit behavioral disturbances, such as agitation, wandering and violent outbursts.

Agitated behaviors can also be manifested in cognitively intact elderly people and by those with psychiatric disorders other than dementia

Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging evidence that agents acting at the 5HT_{2A} receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I.R., et al., J Clin Psychiatry 1999 Feb., 60(2):107-115; and Street, J.S., et al., Arch Gen Psychiatry 2000 Oct., 57(10):968-976).

The compounds of the invention disclosed herein are useful for treating agitation and symptoms thereof. Thus, in some embodiments, the present invention provides methods for treating agitation in an individual in need of such treatment comprising administering to the individual a composition comprising a 5HT_{2A} inverse agonist disclosed herein. In some embodiments, the agitation is due to a psychiatric disorder other than dementia. In some embodiments, the present invention provides methods for treatment of agitation or a symptom thereof in an individual suffering from dementia comprising administering to the individual a composition comprising a 5HT_{2A} inverse agonist disclosed herein. In some embodiments of such methods, the dementia is due to a degenerative disease of the nervous system, for example and without limitation, Alzheimers disease, Lewy Body, Parkinson's disease, and Huntington's disease, or dementia due to diseases that affect blood vessels, including with out limitation stroke and multi-infarct dementia. In some embodiments, methods are provided for treating agitation or a symptom thereof in an individual in need of such treatment, where the individual is a cognitively intact elderly patient, comprising administering to the individual a composition comprising a 5HT_{2A} inverse agonist disclosed herein.

4. ADD-ON THERAPY TO HALOPERIDOL IN THE TREATMENT OF SCHIZOPHRENIA AND OTHER DISORDERS:

Schizophrenia is a psychopathic disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by a number of characteristics, psychotic symptoms, progression, phasic development and deterioration in social behavior and professional capability in the region below the highest level ever attained. Characteristic psychotic symptoms are disorders of thought content (multiple, fragmentary, incoherent, implausible or simply delusional contents or ideas of persecution) and of mentality (loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (hallucinations), of emotions (superficial or inadequate emotions), of self-perception, of intentions and impulses, of interhuman relationships, and finally psychomotoric disorders (such as catatonia). Other symptoms are also associated with this disorder. (See, American Statistical and Diagnostic Handbook).

Haloperidol (Haldol) is a potent dopamine D2 receptor antagonist. It is widely prescribed for acute schizophrenic symptoms, and is very effective for the positive symptoms of schizophrenia. However, Haldol is not effective for the negative symptoms of schizophrenia and may actually induce negative symptoms as well as cognitive dysfunction. In accordance with some methods of the invention, adding a 5HT_{2A} inverse agonist concomitantly with Haldol will provide benefits including the ability to use a lower dose of Haldol without losing its effects on positive symptoms, while reducing or eliminating its inductive effects on negative symptoms, and prolonging relapse to the individual's next schizophrenic event.

Haloperidol is used for treatment of a variety of behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS). Further uses include in the treatment of infantile autism, Huntington's chorea, and nausea and vomiting from chemotherapy and chemotherapeutic antibodies. Administration of 5HT_{2A} inverse agonists disclosed herein with haloperidol also will provide benefits in these indications.

In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to the individual a dopamine D2 receptor antagonist and a 5HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to the individual haloperidol and a 5HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the individual a dopamine D2 receptor antagonist and a 5HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the individual haloperidol and a 5HT_{2A} inverse agonist disclosed herein.

In further embodiments, the present invention provides methods for treating schizophrenia in an individual in need of said treatment comprising administering to the individual a dopamine D2 receptor antagonist and a 5HT_{2A} inverse agonist disclosed herein. Preferably, the dopamine D2 receptor antagonist is haloperidol.

The administration of the dopamine D2 receptor antagonist can be concomitant with administration of the 5HT_{2A} inverse agonist, or they can be administered at different times. Those of skill in the art will easily be able to determine appropriate dosing regimes for the most efficacious reduction or elimination of deleterious haloperidol effects. In some embodiments, haloperidol and the 5HT_{2A} inverse agonist are administered in a single dosage form, and in other embodiments, they are administered in separate dosage forms.

The present invention further provides methods of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to an individual suffering from said schizophrenia, comprising administering to the individual a 5HT_{2A} inverse agonist as disclosed herein.

5. SLEEP DISORDERS

It is reported in the National Sleep Foundation's 2002 Sleep In America Poll, more than one-half of the adults surveyed (58%) report having experienced one or more symptoms of insomnia at least a few nights a week in the past year. Additionally, about three in ten (35%) say they have experienced insomnia-like symptoms every night or almost every night.

The normal sleep cycle and sleep architecture can be disrupted by a variety of organic causes as well as environmental influences. According to the International Classification of

Sleep Disorders, there are over 80 recognized sleep disorders. Of these, compounds of Formula (I) are effective, for example, in any one or more of the following sleep disorders (ICSD – International Classification of Sleep Disorders: Diagnostic and Coding Manual. *Diagnostic Classification Steering Committee*, American Sleep Disorders Association, 1990):

A. DYSSOMNIAS

a. Intrinsic Sleep Disorders:

Psychophysiological insomnia, Sleep state misperception, Idiopathic insomnia, Obstructive sleep apnea syndrome, Central sleep apnea syndrome, Central alveolar hypoventilation syndrome, Periodic limb movement disorder, Restless leg syndrome and Intrinsic sleep disorder NOS.

b. Extrinsic Sleep Disorders:

Inadequate sleep hygiene, Environmental sleep disorder, Altitude insomnia, Adjustment sleep disorder, Insufficient sleep syndrome, Limit-setting sleep disorder, Sleep-onset association disorder, Nocturnal eating (drinking) syndrome, Hypnotic dependent sleep disorder, Stimulant-dependent sleep disorder, Alcohol-dependent sleep disorder, Toxin-induced sleep disorder and Extrinsic sleep disorder NOS.

c. Circadian Rhythm Sleep Disorders:

Time zone change (jet lag) syndrome, Shift work sleep disorder, Irregular sleep-wake pattern, Delayed sleep phase syndrome, Advanced sleep phase syndrome, Non-24-hour sleep-wake disorder and Circadian rhythm sleep disorder NOS.

B. PARASOMNIAS

a. Arousal Disorders:

Confusional arousals, Sleepwalking and Sleep terrors.

b. Sleep-Wake Transition Disorders:

Rhythmic movement disorder, Sleep starts, Sleep talking and Nocturnal leg cramps.

C. SLEEP DISORDERS ASSOCIATED WITH MEDICAL/PSYCHIATRIC DISORDERS

a. Associated with Mental Disorders:

Psychoses, Mood disorders, Anxiety disorders, Panic disorders and Alcoholism.

b. Associated with Neurological Disorders:

Cerebral degenerative disorders, Dementia, Parkinsonism, Fatal familial insomnia, Sleep-related epilepsy, Electrical status epilepticus of sleep and Sleep-related headaches.

c. Associated with Other Medical Disorders:

Sleeping sickness, Nocturnal cardiac ischemia, Chronic obstructive pulmonary disease Sleep-related asthma, Sleep-related gastroesophageal reflux, Peptic ulcer disease, Fibrositis syndrome, Osteoarthritis, Rheumatoid arthritis, Fibromyalgia and Post-surgical.

The effects of sleep deprivation are more than excessive daytime sleepiness. Chronic insomniacs report elevated levels of stress, anxiety, depression and medical illnesses (National Institutes of Health, National Heart, Lung, and Blood Institute, *Insomnia Facts Sheet*, Oct. 1995). Preliminary evidence suggests that having a sleep disorder that causes significant loss of sleep may contribute to increased susceptibility to infections due to immunosuppression, cardiovascular complications such as hypertension, cardiac arrhythmias, stroke, and myocardial infarction. Compounds of Formula (I) are useful to prevent or alleviate these complications by improving sleep quality.

The most common class of medications for the majority of sleep disorders are the benzodiazepines, but the adverse effect profile of benzodiazepines include daytime sedation, diminished motor coordination, and cognitive impairments. Furthermore, the National Institutes of Health Consensus conference on Sleeping Pills and Insomnia in 1984 have developed guidelines discouraging the use of such sedative-hypnotics beyond 4-6 weeks because of concerns raised over drug misuse, dependency, withdrawal and rebound insomnia. Therefore, it is desirable to have a pharmacological agent for the treatment of insomnia, which is more effective and/or has fewer side effects than those currently used.

Clinical studies with agents of a similar mechanism of action as are compounds of Formula (I) have demonstrated significant improvements on objective and subjective sleep parameters in normal, healthy volunteers as well as patients with sleep disorders and mood disorders [Sharpely AL, et al. Slow Wave Sleep in Humans: Role of 5HT_{2A} and 5HT_{2c} Receptors. *Neuropharmacology*, 1994, Vol. 33(3/4):467-71; Winokur A, et al. Acute Effects of Mirtazapine on Sleep Continuity and Sleep Architecture in Depressed Patients: A Pilot Study. *Soc of Biol Psych*, 2000, Vol. 48:75-78; and Landolt HP, et al. Serotonin-2 Receptors and Human Sleep: Effect of Selective Antagonist on EEG Power Spectra. *Neuropsychopharmacology*, 1999, Vol. 21(3):455-66].

Some sleep disorders are sometimes found in conjunction with other conditions and accordingly those conditions are treatable by compounds of Formula (I). For example but not limiting, patients suffering from mood disorders typically suffer from a sleep disorder that can be treatable by compounds of Formula (I). Having one pharmacological agent which treats two or

more existing or potential conditions, as does the present invention, is more cost effective, leads to better compliance and has fewer side effects than taking two or more agents.

It is an object of the present invention to provide a therapeutic agent for the use in treating Sleep Disorders. It is another object of the present invention to provide one pharmaceutical agent, which may be useful in treating two or more conditions wherein one of the conditions is a sleep disorder. Compounds of Formula (I) described herein may be used alone or in combination with a mild sleep inducer (i.e. antihistamine).

SLEEP ARCHITECTURE

Sleep comprises two physiological states: Non rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep consists of four stages, each of which is characterized by progressively slower brain wave patterns, with the slower patterns indicating deeper sleep. So-called delta sleep, stages 3 and 4 of NREM sleep, is the deepest and most refreshing type of sleep. Many patients with sleep disorders are unable to adequately achieve the restorative sleep of stages 3 and 4. In clinical terms, patients' sleep patterns are described as fragmented, meaning the patient spends a lot of time alternating between stages 1 and 2 (semi-wakefulness) and being awake and very little time in deep sleep. Compounds of Formula (I) described are effective in consolidating sleep patterns so that the patient with previously fragmented sleep can now achieve restorative, delta-wave sleep for longer, more consistent periods of time.

As sleep moves from stage 1 into later stages, heart rate and blood pressure drop, metabolic rate and glucose consumption fall, and muscles relax. NREM sleep makes up about 75% of total sleep time; stage 1 accounting for 5-10% of total sleep time, stage 2 for about 45-50%, stage 3 approximately 12%, and stage 4 13-15%. About 90 minutes after sleep onset, NREM sleep gives way to the first REM sleep episode of the night. REM makes up approximately 25% of total sleep time. In contrast to NREM sleep, REM sleep is characterized by high pulse, respiration, and blood pressure, as well as other physiological patterns similar to those seen in the active waking stage. Hence, REM sleep is also known as "paradoxical sleep." Sleep onset usually occurs during NREM sleep and takes 10-20 minutes in healthy young adults. The four stages of NREM sleep together with a REM phase form one complete sleep cycle that is repeated throughout the duration of sleep, usually four or five times. The cyclical nature of sleep is regular and reliable; a REM period occurs about every 90 minutes during the night. However, the first REM period tends to be the shortest, often lasting less than 10 minutes, whereas the later REM periods may last up to 40 minutes. With aging, the time between retiring and sleep onset increases and the total amount of night-time

sleep decreases because of changes in sleep architecture that impair sleep maintenance as well as sleep quality. Both NREM (particularly stages 3 and 4) and REM sleep are reduced. However, stage 1 NREM sleep, which is the lightest sleep, increases with age.

SUBJECTIVE AND OBJECTIVE DETERMINATIONS OF SLEEP DISORDERS

There are a number of ways to determine whether the onset, duration or quality of sleep (e.g. non-restorative or restorative sleep) is impaired or improved. One method is a subjective determination of the patient, e.g., do they feel drowsy or rested upon waking. Other methods involve the observation of the patient by another during sleep, e.g., how long it takes the patient to fall asleep, how many times does the patient wake up during the night, how restless is the patient during sleep, etc. Another method is to objectively measure the stages of sleep.

Polysomnography is the monitoring of multiple electrophysiological parameters during sleep and generally includes measurement of EEG activity, electroculographic activity and electromyographic activity, as well as other measurements. These results, along with observations, can measure not only sleep latency (the amount of time required to fall asleep), but also sleep continuity (overall balance of sleep and wakefulness) and sleep consolidation (percent of sleeping time spent in delta-wave or restorative sleep) which may be an indication of the quality of sleep.

There are five distinct sleep stages, which can be measured by polysomnography: rapid eye movement (REM) sleep and four stages of non-rapid eye movement (NREM) sleep (stages 1, 2, 3 and 4). Stage 1 NREM sleep is a transition from wakefulness to sleep and occupies about 5% of time spent asleep in healthy adults. Stage 2 NREM sleep, which is characterized by specific EEG waveforms (sleep spindles and K complexes), occupies about 50% of time spent asleep. Stages 3 and 4 NREM sleep (also known collectively as slow-wave sleep and delta-wave sleep) are the deepest levels of sleep and occupy about 10-20% of sleep time. REM sleep, during which the majority of vivid dreams occur, occupies about 20-25% of total sleep.

These sleep stages have a characteristic temporal organization across the night. NREM stages 3 and 4 tend to occur in the first one-third to one-half of the night and increase in duration in response to sleep deprivation. REM sleep occurs cyclically through the night. Alternating with NREM sleep about every 80-100 minutes. REM sleep periods increase in duration toward the morning. Human sleep also varies characteristically across the life span. After relative stability with large amounts of slow-wave sleep in childhood and early adolescence, sleep continuity and depth deteriorate across the adult age range. This

deterioration is reflected by increased wakefulness and stage 1 sleep and decreased stages 3 and 4 sleep.

Accordingly, another aspect of the present invention relates to the therapeutic use of compounds of Formula (I) for the treatment of Sleep Disorders. Compounds of Formula (I) are potent inverse agonists at the serotonin 5HT₂ receptors and are effective in the treatment of Sleep Disorders by promoting one or more of the following: reducing the sleep onset latency period (measure of sleep induction), reducing the number of nighttime awakenings, and prolonging the amount of time in delta-wave sleep (measure of sleep quality enhancement) without effecting REM sleep. In addition, compounds of Formula (I) are effective either as a monotherapy or in combination with sleep inducing agents, for example but not limiting, antihistamines.

Pharmaceutical Compositions

Suitable pharmaceutically-acceptable carriers are available to those in the art; for example, see Remington: The Science and Practice of Pharmacy, 20th Edition, 2000, Lippincott, Williams & Wilkins, (Gennaro et al., eds.).

While it is possible that, for use in the prophylaxis or treatment, a compound of the invention may in an alternative use be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in

conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The dose when using the compounds of Formula (I) can vary within wide limits, and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the individual, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the Formula (I). Representative doses of the present invention include, about 0.01 mg to about 1000 mg, about 0.01 to about 750 mg, about 0.01 to about 500 mg, 0.01 to about 250 mg, 0.01 mg to about 200 mg, about 0.01 mg to 150 mg, about 0.01 mg to about 100 mg, and about 0.01 mg to about 75 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4, doses. If appropriate, depending on individual behavior and as appropriate from the individuals physician or care-giver it may be necessary to deviate upward or downward from the daily dose.

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the individual and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system, typically an animal model, to another, such as a human. An illustrative but not intended to be limiting *in vivo* animal model is provided as an Example *infra*. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the individual, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the Formula (I) and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors as cited above. Thus, the actual dosage regimen employed may vary widely and

therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4, part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt, solvate or hydrate of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desired shape and size.

The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are necessary. Suitable carriers for powders and tablets include, for example, magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the individual administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the Formula (I) or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the Formula (I) as an aerosol can be prepared by processes well-known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the Formula (I) in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others, and, if appropriate, customary propellants, for example include carbon dioxide, CFC's, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a

surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

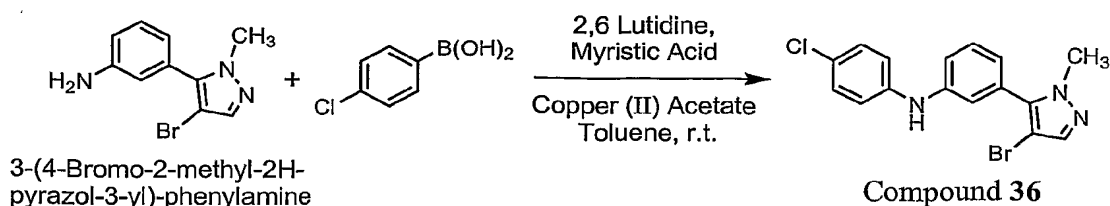
Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

EXAMPLES

The following Examples are provided for illustrative purposes and not as a means of limitation.

Example 1

Method A: Synthesis of Compound 36, [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-chloro-phenyl)-amine, using Copper (II) Acetate and 4-Chlorophenyl Boronic acid.

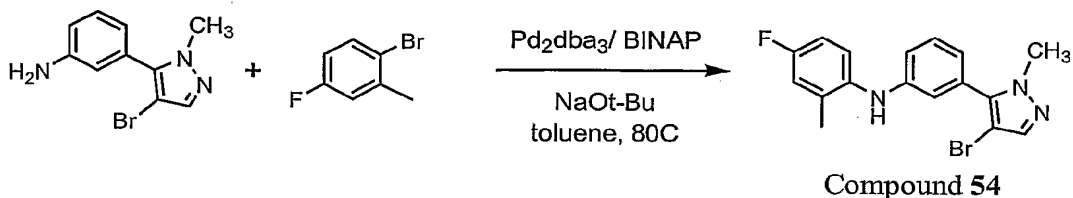


A 3-L three-neck round bottom flask was flushed with argon and filled with ~ 200 mL of toluene. Under argon, copper acetate (2.23 g, 12.25 mmol, 0.20 eq.), myristic acid (4.20 g, 18.38 mmol, 0.30 eq.), and *p*-chlorophenylboronic acid (19.1616 g, 122.54 mmol, 2.0 eq.) was added and stirred at room temperature with an oversized stir bar for ten minutes. While mixing, 2,6-lutidine (7.14 mL, 61.27 mmol, 1.0 eq.) was added via syringe and allowed to stir for an additional 10 minutes which enhanced solubility of the reaction mixture. 3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamine (15.45 g, 61.27 mmol, 1.0 eq.) was then added and a needle was used to bubble dry air into the reaction mixture overnight. The following evening an additional equivalent of the boronic acid, copper acetate, myristic acid and 2,6-lutidine was added as described above. The reaction mixture was monitored via LC-MS and thin layer chromatography using dichloromethane as the eluent.

The reaction mixture was extracted with a mixture of 4 volumes ethyl acetate, 1.5 volumes of NH_4OH , 0.5 volumes of water and brine. In this mixture an ammonium salt was suspended in the organic layer and as such was filtered off using a Büchner funnel. The ethyl acetate layer was washed twice with NH_4OH and once with distilled water. Sodium sulfate was used to dry the organic layer and the ethyl acetate was removed to yield a crude yellow oil. This product was then purified twice using column chromatography (Biotage 65 M column) with a gradient of 0-5% hexanes in dichloromethane. A third chromatography step was required using a gradient of 10-25% ethyl acetate in hexanes to yield 13.954 g (63% yield) of Compound 36 as an off-white crystalline solid. LCMS m/z (%) = 362.0 (MH^+ ^{79}Br , 100), 364 (MH^+ ^{81}Br , 97). ^1H NMR (400 MHz, DMSO-d_6): δ 8.54 (s, 1H), 7.64 (s, 1H), 7.41 (dd, J = 7.9, 1H), 7.29 (dd, J = 9.9, 5.3 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.18-7.10 (m, 3H), 7.13 (d, J = 8.9 Hz, 1H) 6.95 (d, J = 7.8 Hz, 1H), 3.79 (s, 3H).

Example 2

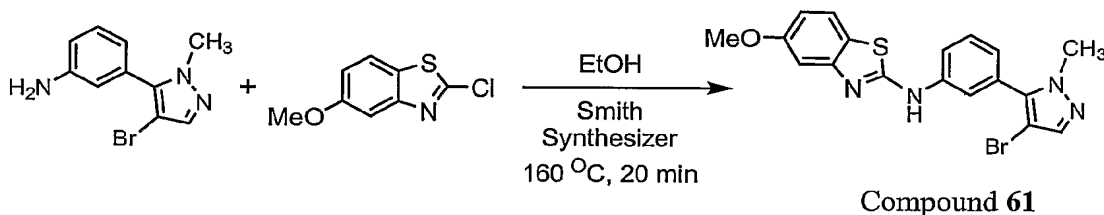
Method B: Synthesis of Compound 54, [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-fluoro-2-methyl-phenyl)-amine, using *tris*(Dibenzylideneacetone)-dipalladium (0) and 2-Bromo-5-Fluorotoluene in the presence of sodium *tert*-butoxide.



A 20-mL scintillation vial was flushed with argon and then charged of anhydrous toluene (2 mL). Sodium tert-butoxide (53.37 mg, 0.56 mmol), tris(dibenzylideneacetone) dipalladium (18.16 mg, 0.40 mmol), 3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamine (0.10 g, 0.40 mmol), 2-bromo-5-fluorotoluene (50.15 μ l, 0.40 mmol) and BINAP (26.48 mg, 0.04 mmol). The reaction was heated and stirred at 80°C for 72 hours under argon atmosphere. The mixture was cooled to ambient temperature, taken up in diethyl ether and ethyl acetate, filtered through celite and concentrated. The crude product was then purified by HPLC. The major peak was collected and one drop of ammonia hydroxide was added to neutralize the acid and lyophilized to produce 74.1 mg (51.4%) of Compound 54 as a tan solid. LCMS m/z (%) = 360 (MH^+ ^{79}Br , 100), 362 (MH^+ ^{81}Br , 97). 1H NMR (400MHz, $CDCl_3$): σ 7.70 (s, 1H), 7.33 (dd, J = 7.8, 7.8 Hz, 1H), 7.21 (dd, J = 8.6, 5.4 Hz, 1H), 6.97 (dd, J = 9.2, 2.8 Hz, 1H), 6.91-9.85 (m, 2H), 6.81 (d, J = 7.6 Hz, 1H) 6.73 (dd, J = 1.8, 1.8 Hz, 1H), 3.84 (s, 3H), 2.27 (s, 3H).

Example 3

Method C: Synthesis of Compound 61, [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(5-methoxy-benzothiazol-2-yl)-amine, using 2-Chloro-6-methoxy-benzothiazole and Microwave Irradiation (Smith Synthesizer).

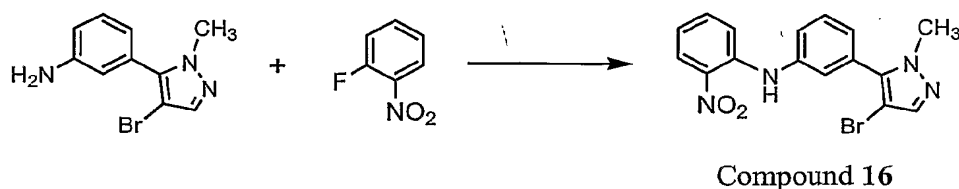


A mixture of 3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenylamine (50 mg, 0.2 mmol) and 2-chloro-6-methoxy-benzothiazole (39.3 mg, 0.2 mmol) in ethanol (1 mL) was heated on a Smith Synthesizer at 160 °C for 20 minutes. The precipitate that formed was collected by filtration and washed with ethanol to provide 56.8 mg (68.6% yield) of Compound 61 as a white solid: LCMS m/z (%) = 415 (MH^+ ^{79}Br , 100), 417 (MH^+ ^{81}Br , 100). 1H NMR (400MHz, $DMSO-d_6$): σ 10.50 (s, 1H), 7.92 (s, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.68 (s, 1H), 7.54-7.50 (m,

2H), 7.46 (d, J = 2.6 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 6.93 (dd, J=8.8, 2.6 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H).

Example 4

Method D: Synthesis of Compound 16, [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2-nitro-phenyl)-amine, using 2-Fluoro-nitrobenzene and heat.

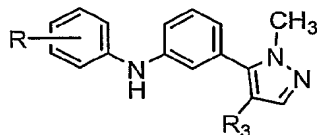


3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamine (359.4 mg, 1.43 mmol, 1 eq) was dissolved in DMA (3 mL) and pyridine (300 μ L). To this solution was added 1-fluoro-2-nitrobenzene (180 μ L, 1.71 mmol, 1.2 eq) and the mixture was heated to 130°C for 36 hours. After cooling to ambient temperature, 1N HCl (20 mL) was added and the mixture extracted with Et₂O (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent evaporated. The residue was then purified by SiO₂ Chromatography (Hex \rightarrow 1:1 Hex/EtOAc gradient elution) to provide 24 mg (5 %) of Compound 16 as an off white solid: LCMS m/z (%) = 373 (MH⁺ ⁷⁹Br, 100), 375 (MH⁺ ⁸¹Br, 97). ¹H NMR (400MHz, CDCl₃): σ 9.55 (s, 1H), 8.22 (d, J=8.4 Hz, 1H), 7.53-7.57 (m, 2H), 7.35-7.42 (m, 3H), 7.23-7.26 (m, 2H), 6.84 (dd, J=7.6, 7.6 Hz, 1H), 3.86 (s, 3H).

Example 5

The following compounds were produced using either Method A, B, C or D or a variation thereof (TABLES 3-4).

TABLE 3



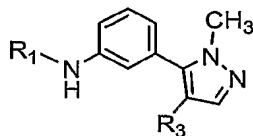
Cmpd No.	R	R ₃	Method	LCMS (m/z)
64	H	Br	A	328 (MH ⁺ ⁷⁹ Br, 100), 330 (MH ⁺ ⁸¹ Br, 100)
17	3-Cl	Br	A	362 (MH ⁺ ⁷⁹ Br, 90), 364 (MH ⁺ ⁸¹ Br, 100)
18	3,5-diCF ₃	Br	A	464 (MH ⁺ ⁷⁹ Br, 100), 466 (MH ⁺ ⁸¹ Br, 90)
37	4-F	Br	A	346 (MH ⁺ ⁷⁹ Br, 60), 348 (MH ⁺ ⁸¹ Br, 100)
38	4-OMe	Br	A	358 (MH ⁺ ⁷⁹ Br, 70), 360 (MH ⁺ ⁸¹ Br, 100)
19	3-OMe	Br	A	358 (MH ⁺ ⁷⁹ Br, 70), 360 (MH ⁺ ⁸¹ Br, 100)
39	3,4-methylenedioxy	Br	A	372 (MH ⁺ ⁷⁹ Br, 100), 374 (MH ⁺ ⁸¹ Br, 80)
40	3-OCF ₃	Br	A	412 (MH ⁺ ⁷⁹ Br, 80), 414 (MH ⁺ ⁸¹ Br, 100)
41	4-Br	Br	A	406 (MH ⁺ ⁷⁹ Br, 50), 408 (MH ⁺ ⁸¹ Br, 100)
20	3,4-diOMe	Br	A	388 (MH ⁺ ⁷⁹ Br, 100), 390 (MH ⁺ ⁸¹ Br, 90)
42	4-SMe	Br	A	374 (MH ⁺ ⁷⁹ Br, 80), 376 (MH ⁺ ⁸¹ Br, 100)
43	4-CN	Br	A	353 (MH ⁺ ⁷⁹ Br, 100), 355 (MH ⁺ ⁸¹ Br, 100)
21	3-COCH ₃	Br	A	370 (MH ⁺ ⁷⁹ Br, 100), 372 (MH ⁺ ⁸¹ Br, 100)
22	3,5-diCl	Br	A	396 (MH ⁺ ⁷⁹ Br, 50), 398 (MH ⁺ ⁸¹ Br, 100)

Cmpd No.	R	R ₃	Method	LCMS (m/z)
23	3,5-diMe	Br	A	356 (MH ⁺ ⁷⁹ Br, 100), 358 (MH ⁺ ⁸¹ Br, 90)
44	4-CF ₃	Br	A	396 (MH ⁺ ⁷⁹ Br, 100), 398 (MH ⁺ ⁸¹ Br, 100)
45	4-OCF ₃	Br	A	412 (MH ⁺ ⁷⁹ Br, 100), 414 (MH ⁺ ⁸¹ Br, 80)
46	4-SO ₂ Me	Br	A	406 (MH ⁺ ⁷⁹ Br, 100), 408 (MH ⁺ ⁸¹ Br, 100)
24	3-NHAc	Br	A	385 (MH ⁺ ⁷⁹ Br, 100), 387 (MH ⁺ ⁸¹ Br, 100)
25	3-CH ₂ OH	Br	A	358 (MH ⁺ ⁷⁹ Br, 90), 360 (MH ⁺ ⁸¹ Br, 100)
47	3-Cl-4-F	Br	A	380 (MH ⁺ ⁷⁹ Br, 80), 382 (MH ⁺ ⁸¹ Br, 100)
48	3,4-diCl	Br	A	396 (MH ⁺ ⁷⁹ Br, 70), 398 (MH ⁺ ⁸¹ Br, 100)
49	3-Me-4-Cl	Br	A	376 (MH ⁺ ⁷⁹ Br, 80), 378 (MH ⁺ ⁸¹ Br, 100)
26	2-Me-4-Cl	Br	A	376 (MH ⁺ ⁷⁹ Br, 80), 378 (MH ⁺ ⁸¹ Br, 100)
50	3,5-diF	Br	A	364 (MH ⁺ ⁷⁹ Br, 100), 366 (MH ⁺ ⁸¹ Br, 100)
51	3-Cl-4-CF ₃	Br	A	430 (MH ⁺ ⁷⁹ Br, 80), 432 (MH ⁺ ⁸¹ Br, 100)
52	3,4-diF	Br	A	364 (MH ⁺ ⁷⁹ Br, 100), 366 (MH ⁺ ⁸¹ Br, 100)
6	4-Cl	Cl	A	318 (MH ⁺ ³⁵ Cl, 100), 320 (MH ⁺ ³⁷ Cl, 60)
7	4-CF ₃	Cl	A	352 (MH ⁺ ³⁵ Cl, 100), 354 (MH ⁺ ³⁷ Cl, 40)
53	3-Me-4-F	Br	A	360 (MH ⁺ ⁷⁹ Br, 90), 362 (MH ⁺ ⁸¹ Br, 100)

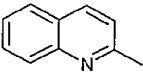
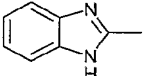
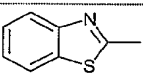
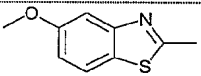
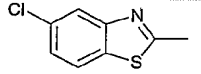
Cmpd No.	R	R ₃	Method	LCMS (m/z)
27	4-OPh	Br	A	420 (MH ⁺ ⁷⁹ Br,100), 422 (MH ⁺ ⁸¹ Br,100)
28	3-CF ₃	Br	A	396 (MH ⁺ ⁷⁹ Br,100), 398 (MH ⁺ ⁸¹ Br,100)
29	3-NO ₂	Br	A	373 (MH ⁺ ⁷⁹ Br,90), 375 (MH ⁺ ⁸¹ Br,100)
30	2,3,4-triOMe	Br	A	418 (MH ⁺ ⁷⁹ Br,100), 420 (MH ⁺ ⁸¹ Br,80)
54	2-Me-4-F	Br	B	360 (MH ⁺ ⁷⁹ Br,90), 362 (MH ⁺ ⁸¹ Br,100)
1	4-Cl	H	A	284 (MH ⁺ ³⁵ Cl,100), 286 (MH ⁺ ³⁷ Cl,50)
2	4-CF ₃	H	A	318 (MH ⁺ ,100)
8	4-OCF ₃	Cl	A	368 (MH ⁺ ³⁵ Cl,100), 370 (MH ⁺ ³⁷ Cl,70)
9	3-OCF ₃	Cl	A	368 (MH ⁺ ³⁵ Cl,100), 370 (MH ⁺ ³⁷ Cl,70)
10	4-F	Cl	A	302 (MH ⁺ ³⁵ Cl,100), 304 (MH ⁺ ³⁷ Cl,50)
3	4-OCF ₃	H	A	334 (MH ⁺ ,100)
4	3-OCF ₃	H	A	334 (MH ⁺ ,100)
5	4-F	H	A	268 (MH ⁺ ,100)
31	3-F-4-Me	Br	A	360 (MH ⁺ ⁷⁹ Br,90), 362 (MH ⁺ ⁸¹ Br,100)
32	2,4-diCF ₃	Br	A	464 (MH ⁺ ⁷⁹ Br,100), 466 (MH ⁺ ⁸¹ Br,90)
33	3-F-4-OMe	Br	A	376 (MH ⁺ ⁷⁹ Br,100), 378 (MH ⁺ ⁸¹ Br,100)

Cmpd No.	R	R ₃	Method	LCMS (m/z)
34	2,3-diF	Br	A	364 (MH ⁺ ⁷⁹ Br,100), 366 (MH ⁺ ⁸¹ Br,100)
35	2,4-diF	Br	B	364 (MH ⁺ ⁷⁹ Br,100), 366 (MH ⁺ ⁸¹ Br,100)
11	3-Me-4-Cl	Cl	A	332 (MH ⁺ ³⁵ Cl,100), 334 (MH ⁺ ³⁷ Cl,70)
12	3-Cl-4-CF ₃	Cl	A	386 (MH ⁺ ³⁵ Cl,100), 388 (MH ⁺ ³⁷ Cl,60)
13	3,4-diF	Cl	A	320 (MH ⁺ ³⁵ Cl,100), 322 (MH ⁺ ³⁷ Cl,40)
14	3-Cl	Cl	A	318 (MH ⁺ ³⁵ Cl,100), 320 (MH ⁺ ³⁷ Cl,60)
15	4-OMe	Cl	A	314 (MH ⁺ ³⁵ Cl,100), 316 (MH ⁺ ³⁷ Cl,40)
65	4-I	Br	A	454 (MH ⁺ ⁷⁹ Br,100), 456 (MH ⁺ ⁸¹ Br,70)
66	2-OMe-5-Me	Br	A	372 (MH ⁺ ⁷⁹ Br,80), 374 (MH ⁺ ⁸¹ Br,100)

TABLE 4

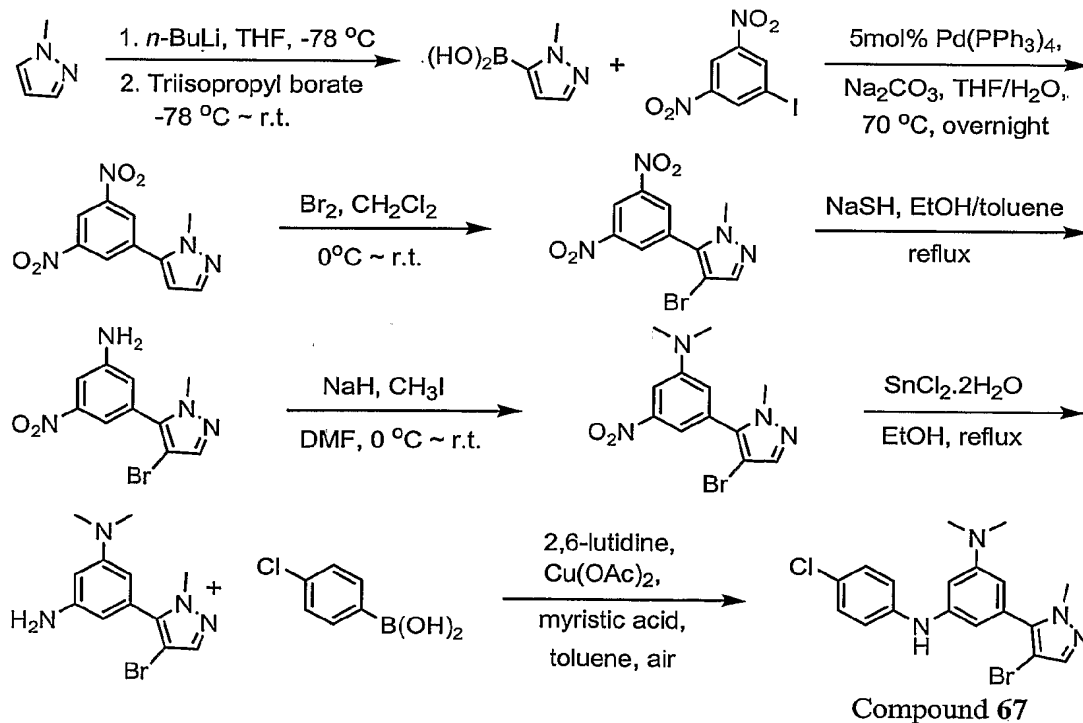


Cmpd No.	R ₁	R ₃	Method	LCMS (m/z)
55	1-naphthyl	Br	A	378 (MH ⁺ ⁷⁹ Br, 100), 380 (MH ⁺ ⁸¹ Br, 100)
56	2-naphthyl	Br	A	378 (MH ⁺ ⁷⁹ Br, 100), 380 (MH ⁺ ⁸¹ Br, 100)
63	3-quinoline	Br	A	379 (MH ⁺ ⁷⁹ Br, 100), 381 (MH ⁺ ⁸¹ Br, 100)
57		Br	C	369 (MH ⁺ ⁷⁹ Br, 100), 371 (MH ⁺ ⁸¹ Br, 100)

Cmpd No.	R ₁	R ₃	Method	LCMS (m/z)
58		Br	C	379 (MH ⁺ ⁷⁹ Br, 100), 381 (MH ⁺ ⁸¹ Br, 100)
59		Br	C	368 (MH ⁺ ⁷⁹ Br, 100), 370 (MH ⁺ ⁸¹ Br, 100)
60		Br	C	385 (MH ⁺ ⁷⁹ Br, 90), 387 (MH ⁺ ⁸¹ Br, 100)
61		Br	C	415 (MH ⁺ ⁷⁹ Br, 100), 417 (MH ⁺ ⁸¹ Br, 100)
62		Br	C	419 (MH ⁺ ⁷⁹ Br, 70), 421 (MH ⁺ ⁸¹ Br, 100)

Example 6

Synthesis of Compound 67 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(*N,N*-dimethylamino)-phenyl]-(4-chloro-phenyl)-amine (Scheme 1):

**SCHEME 1**

Compound **67** was prepared in an analogous method as described by **Method A** using 4-chlorophenylboronic acid and 5-(4-bromo-2-methyl-2H-pyrazol-3-yl)-*N,N*-dimethyl-benzene-1,3-diamine in 25% yield: LCMS m/z (%) = 405 (MH^+ ^{79}Br , 75), 407 (MH^+ ^{81}Br , 100). 1H NMR (400 MHz, $CDCl_3$) δ : 7.50 (s, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.42 (t, J = 2.1 Hz, 1H), 6.40 (t, J = 1.6 Hz, 1H), 6.29 (dd, J = 1.5, 2.3 Hz, 1H), 3.84 (s, 3H), 2.97 (s, 6H).

Intermediate 5-(4-bromo-2-methyl-2H-pyrazol-3-yl)-*N,N*-dimethyl-benzene-1,3-diamine was prepared by the following steps:

1) 2-Methyl-2H-pyrazole-3-boronic acid

To a stirred solution of 1-methylpyrazole (19.80 g, 0.24 mol) in THF (500 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 116 mL, 0.29 mol, 1.2 eq.) slowly within 30 mins and the mixture was stirred at this temperature for an additional 1.5 hr. Triisopropyl borate (223.0 mL, 181.40 g, 0.96 mmol, 4.0 eq.) was then added dropwise at -78 °C, followed by stirring overnight until it was warmed up to r.t.. The reaction mixture was acidified to pH = 6 with 1N HCl, THF was removed under vacuum and the aqueous residue was extracted with EtOAc (5 \times 400 mL). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The resultant white solid 2-methyl-2H-pyrazole-3-boronic acid was used without further purification in the subsequent Suzuki cross-coupling step: LCMS m/z (%) = 127 (MH^+ , 100). 1H NMR (400 MHz, CD_3OD) δ : 7.38 (s, 1H), 6.57 (d, J = 4.0 Hz, 1H), 3.81 (s, 3H).

2) 5-(3,5-Dinitro-phenyl)-1-methyl-1H-pyrazole

A mixture of 1-iodo-3,5-dinitrobenzene (1.200g, 4.00 mmol), 2-methyl-2H-pyrazole-3-boronic acid (90%, 1.679g, 10.00mmol, 3.0 eq.) and Na_2CO_3 (6.783g, 64.00 mmol, 16.0 eq.) was dissolved in THF (100 mL) and H_2O (75 mL). The mixture was degassed with N_2 for 5 mins. $Pd(PPh_3)_4$ (0.233g, 0.20 mmol, 0.05 eq.) was then added, the solution was degassed for an additional 5 mins and the mixture was stirred at 70 °C overnight. After consumption of the starting material, the reaction mixture was diluted with EtOAc (100mL), and the aqueous phase was extracted with EtOAc three times (3 \times 100 mL). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The crude reaction mixture was purified by SiO_2 column chromatography (Eluent: EtOAc/Hexane = 1/3 then 1/1) providing 5-(3,5-dinitro-phenyl)-1-methyl-1H-pyrazole (0.937g, 3.78 mmol) in 90% yield: LCMS m/z (%) = 249 (MH^+ , 100). 1H NMR (400 MHz, $CDCl_3$) δ : 9.08 (t, J = 2.0 Hz, 1H), 8.63 (s, 1H), 8.62 (s, 1H), 7.61 (d, J = 2.0 Hz, 1H), 6.55 (d, J = 1.8 Hz, 1H), 4.01 (s, 3H).

3) 4-Bromo-5-(3,5-dinitro-phenyl)-1-methyl-1H-pyrazole

To a stirred solution of 5-(3,5-dinitro-phenyl)-1-methyl-1H-pyrazole (5.33 g, 21.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added dropwise Br_2 (3.77 g, 1.21 mL, 24.0 mmol, 1.1 eq.), the mixture was stirred at 0 °C until the starting material disappeared. The mixture was diluted with EtOAc (200 mL), washed sequentially with saturated NaHCO_3 and saturated $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous phase was extracted with EtOAc (3×60 mL), the combined organic phase was washed with brine, dried over anhydrous MgSO_4 , filtered and evaporated. The crude reaction mixture was triturated with EtOH to provide 4-bromo-5-(3,5-dinitro-phenyl)-1-methyl-1H-pyrazole (4.30 g, 13.0 mmol, 62%) which was directly used in the next selective mono-reduction: LCMS m/z (%) = 327 (MH^+ ^{79}Br , 80), 329 (MH^+ ^{81}Br , 100). ^1H NMR (400 MHz, CDCl_3) δ : 9.17 (t, J = 2.0 Hz, 1H), 8.68 (s, 1H), 8.67 (s, 1H), 7.65 (s, 1H), 3.96 (s, 3H).

4) 3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-nitro-phenylamine:

To a stirred solution of 4-bromo-5-(3,5-dinitro-phenyl)-1-methyl-1H-pyrazole (4.258 g, 13.0 mmol) in a mixture of methanol/toluene (200 mL/40 mL) at 70 °C was added NaSH in methanol (1.824 g/50 mL, 32.5 mmol, 2.5 eq.) within 45 mins, and the reaction mixture was stirred at this temperature for another 30 mins. The solvent was removed under vacuum, the residue was dissolved in EtOAc, and washed with water and brine. It was dried over anhydrous MgSO_4 , filtered and evaporated. The crude reaction mixture was purified by SiO_2 column chromatography (Eluent: EtOAc/Hexane = 1/3 then 1/1) to give 3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-nitro-phenylamine (3.690 g, 12.0 mmol) in 96% yield: LCMS m/z (%) = 297 (MH^+ ^{79}Br , 100), 299 (MH^+ ^{81}Br , 85). ^1H NMR (400 MHz, CDCl_3) δ : 7.62 (s, 1H), 7.60 (s, 1H), 7.57 (s, 1H), 6.99 (s, 1H), 3.87 (s, 3H).

5) [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-nitro-phenyl]-dimethyl-amine:

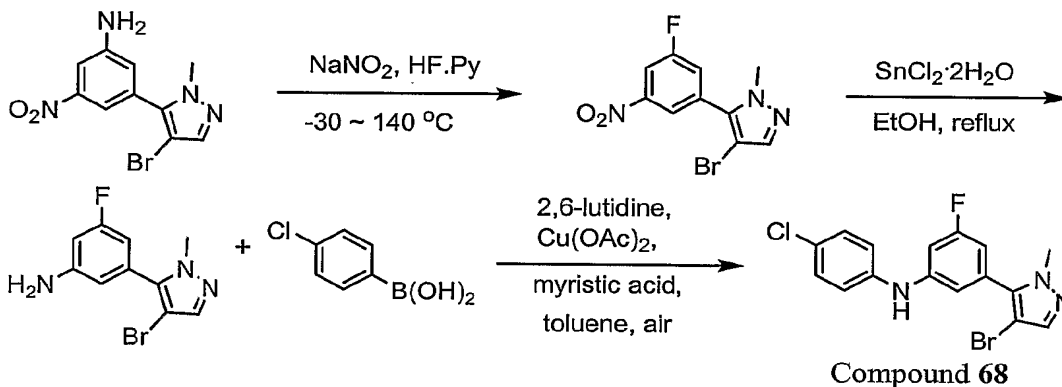
To a stirred solution of 3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-nitro-phenylamine (0.499 g, 1.65 mmol) in DMF (5 mL) at 0 °C was added NaH (60%, 0.264 g, 6.59 mmol, 4.0 eq.) with stirring for 30 mins. CH_3I (0.962 g, 0.42 mL, 6.71 mmol, 4.1 eq.) was added, and the reaction mixture was stirred at this temperature for another 30 mins before warming up to room temperature. The reaction was quenched with EtOH (0.1 mL) and saturated NH_4Cl and extracted with EtOAc (3×20 mL). The combined organic phase was washed with brine, dried over anhydrous MgSO_4 , filtered and evaporated. The crude reaction mixture was purified by SiO_2 column chromatography (Eluent: EtOAc/Hexane = 1/3) to give [3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-nitro-phenyl]-dimethyl-amine (0.181 g, 0.56 mmol, 33%): LCMS m/z (%) = 325 (MH^+ ^{79}Br , 100), 327 (MH^+ ^{81}Br , 85). ^1H NMR (400 MHz, CDCl_3) δ : 7.63 (s, 1H), 7.61 (s, 1H), 7.57 (s, 1H), 6.98 (s, 1H), 3.87 (s, 3H), 3.14 (s, 6H).

6) 5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-*N,N*-dimethyl-benzene-1,3-diamine:

To a stirred solution of [3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-nitro-phenyl]-dimethyl-amine (0.180 g, 0.55 mmol) in EtOH (5 mL) was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.509 g, 2.21 mmol, 4.0 eq.) and the mixture was stirred at reflux for 2 hrs. Ethanol was removed under vacuum and the resultant residue was diluted with EtOAc (20 mL), and washed with saturated NaHCO_3 . The milky aqueous phase was extracted with EtOAc (3×20 mL), the combined organic phase was dried over anhydrous MgSO_4 , filtered and evaporated. After purification by SiO_2 column chromatography (Eluent: EtOAc/Hexane = 1/3 then 1/1), 5-(4-bromo-2-methyl-2H-pyrazol-3-yl)-*N,N*-dimethyl-benzene-1,3-diamine (0.042 g, 0.14 mmol) was obtained in 25% yield: LCMS m/z (%) = 295 ($\text{MH}^+ {}^{79}\text{Br}$, 95), 297 ($\text{MH}^+ {}^{81}\text{Br}$, 100). ^1H NMR (400 MHz, CDCl_3) δ : 7.49 (s, 1H), 6.06 (t, $J = 1.9$ Hz, 1H), 6.04 (t, $J = 2.4$ Hz, 1H), 5.98 (t, $J = 1.5$ Hz, 1H), 3.75 (s, 3H), 2.88 (s, 6H).

Example 7

Synthesis of Compound 68 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-(4-chloro-phenyl)-amine (Scheme 2):



Scheme 2

Compound 68 was prepared in an analogous method as described by **Method A** using 4-chlorophenylboronic acid and 3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenylamine in 67% yield: LCMS m/z (%) = 380 ($\text{MH}^+ {}^{79}\text{Br}$, 75), 382 ($\text{MH}^+ {}^{81}\text{Br}$, 100). ^1H NMR (400 MHz, CDCl_3) δ : 7.52 (s, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.08 (d, $J = 8.0$ Hz, 2H), 6.74-6.82 (m, 2H), 6.61 (ddd, $J = 1.5, 2.2, 8.7$ Hz, 1H), 5.98 (broad s, 1H), 3.83 (s, 3H).

Intermediate 3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenylamine was prepared by the following steps:

1) 4-Bromo-5-(3-fluoro-5-nitro-phenyl)-1-methyl-1H-pyrazole:

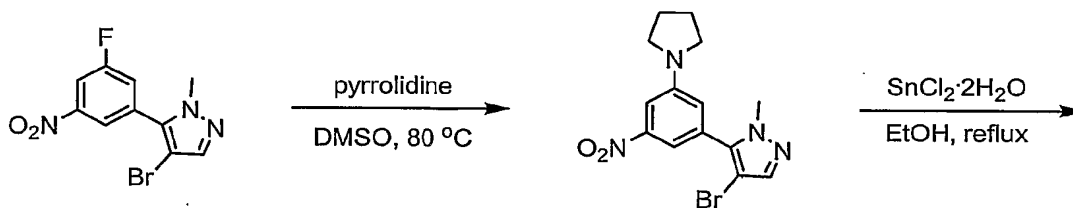
At 0°C, HF·Py (6 mL) was added to 3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-nitro-phenylamine (1.037 g, 3.49 mmol) dropwise with stirring for 10 mins, then warmed up to r.t. and stirred an additional 30 mins. NaNO₂ (0.265g, 3.84 mmol, 1.1 eq.) was added at -30°C, and the mixture was stirred at this temperature for 30 mins, it was then heated to 140°C and stirred for an additional 10 mins. The reaction mixture was cooled to r.t., diluted with EtOAc, washed with water and saturated NaHCO₃ and the aqueous phase was extracted with EtOAc (3×100mL). The combined organic phase was washed with brine, dried over anhydrous MgSO₄, filtered and evaporated. The crude reaction mixture was purified by SiO₂ column chromatography (Eluent: EtOAc/Hexane = 1/5 then 1/3), and 4-bromo-5-(3-fluoro-5-nitro-phenyl)-1-methyl-1H-pyrazole (0.746g, 2.48 mmol, 71%) was obtained: LCMS m/z (%) = 300 (MH⁺ ⁷⁹Br, 100), 302 (MH⁺ ⁸¹Br, 98). ¹H NMR (400 MHz, CDCl₃) δ: 8.13 (s, 1H), 8.05 (dt, *J* = 2.1, 7.8 Hz, 1H), 7.58 (s, 1H), 7.52 (ddd, *J* = 1.5, 2.5, 7.1 Hz, 1H), 3.89 (s, 3H).

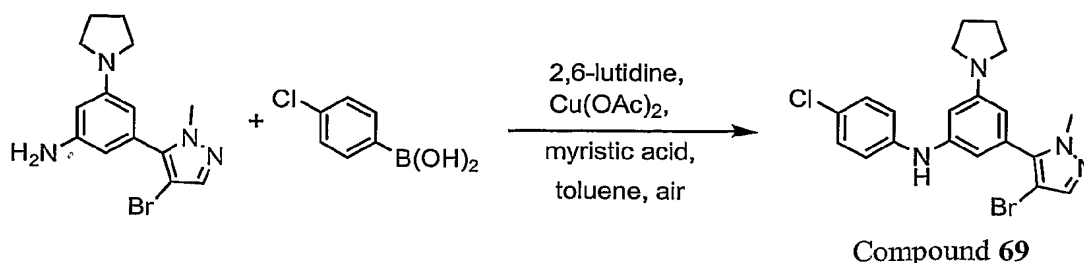
2) 3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenylamine:

To a stirred solution of 4-bromo-5-(3-fluoro-5-nitro-phenyl)-1-methyl-1H-pyrazole (0.524 g, 1.75 mmol) in EtOH (10 mL) was added SnCl₂·2H₂O (1.608 g, 6.98 mmol, 4.0 eq.), the mixture was stirred at reflux for 2 hrs, and EtOH was removed under vacuum. The resultant solid was dissolved in EtOAc, 1N NaOH was added, and the mixture was stirred overnight. The white precipitate was filtered off through celite, and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phase was dried over anhydrous MgSO₄, filtered and evaporated. The crude reaction mixture was purified by SiO₂ column chromatography (Eluent: EtOAc/Hexane = 1/3) to give 3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenylamine (0.450 g, 1.67 mmol, 95%) as white solid: LCMS m/z (%) = 270 (MH⁺ ⁷⁹Br, 100), 272 (MH⁺ ⁸¹Br, 80). ¹H NMR (400 MHz, CDCl₃) δ: 7.50 (s, 1H), 6.46 (d, *J* = 1.8 Hz, 1H), 6.44 (s, 2H), 5.84-3.96 (broad s, 2H), 3.80 (s, 3H).

Example 8

Synthesis of Compound 69 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-(4-chloro-phenyl)-amine (Scheme 3):





Scheme 3

Compound **69** was prepared in an analogous method as described by **Method A** using 4-chlorophenylboronic acid and 3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenylamine in 71% yield by the method A: LCMS m/z (%) = 431 (MH^+ ^{79}Br , 50), 433 (MH^+ ^{81}Br , 100). 1H NMR (400 MHz, $CDCl_3$) δ : 7.50 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.33 (t, J = 1.6 Hz, 1H), 6.27 (t, J = 2.3 Hz, 1H), 6.14 (t, J = 1.6 Hz, 1H), 5.74 (s, 1H), 3.84 (s, 3H), 3.21 (t, J = 6.7 Hz, 4H), 2.01 (dt, J = 3.3, 7.0 Hz, 4H).

Intermediate 3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenylamine was prepared by the following steps:

1) 4-Bromo-1-methyl-5-(3-nitro-5-pyrrolidin-1-yl-phenyl)-1H-pyrazole:

To a stirred solution of 4-Bromo-5-(3-fluoro-5-nitro-phenyl)-1-methyl-1H-pyrazole (0.217 g, 0.72 mmol) in DMSO (5 mL) was added pyrrolidine (0.25 mL, 0.207 g, 2.89 mmol, 4.0 eq.) and the mixture was stirred at 80°C for 2 hrs, then cooled down to room temperature and diluted with EtOAc. It was washed with 1N HCl, water and brine, then dried over $MgSO_4$, filtered and evaporated. The crude reaction mixture was purified by SiO_2 column chromatography (Eluent: EtOAc/Hexane = 1/3) to give compound 4-bromo-1-methyl-5-(3-nitro-5-pyrrolidin-1-yl-phenyl)-1H-pyrazole (0.269g, 0.77 mmol, 89%): LCMS m/z (%) = 351 (MH^+ ^{79}Br , 100), 353 (MH^+ ^{81}Br , 90). 1H NMR (400 MHz, $CDCl_3$) δ : 7.55 (d, J = 4.0 Hz, 1H), 7.45 (s, 1H), 7.41 (s, 1H), 6.80 (t, J = 1.8 Hz, 1H), 3.86 (s, 3H), 3.32 (t, J = 6.7 Hz, 4H), 2.02 (dt, J = 3.3, 6.6 Hz, 4H).

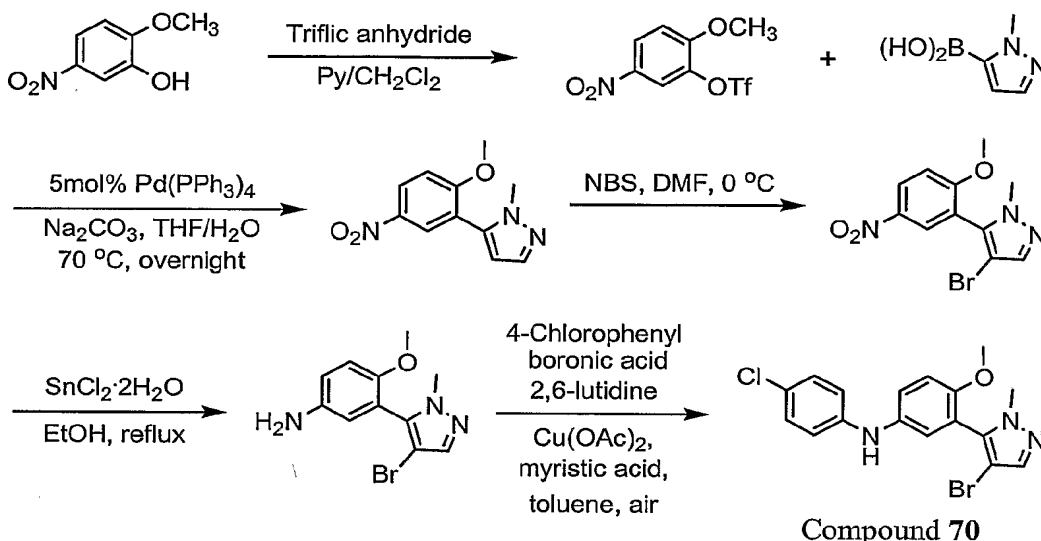
2) 3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenylamine:

To a stirred solution of 4-bromo-1-methyl-5-(3-nitro-5-pyrrolidin-1-yl-phenyl)-1H-pyrazole (0.249 g, 0.71 mmol) in EtOH (10 mL) was added $SnCl_2 \cdot 2H_2O$ (0.653 g, 2.84 mmol, 4.0 eq.), the mixture was stirred at reflux for 2 hrs, and EtOH was removed under vacuum. The resultant solid was dissolved in EtOAc, 1N NaOH was added, and the mixture was stirred overnight. The white precipitate was filtered off through celite, and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude reaction mixture was purified by SiO_2 column chromatography (Eluent: EtOAc/Hexane = 1/3 then 1/1) to give 3-(4-bromo-2-methyl-2H-

pyrazol-3-yl)-5-pyrrolidin-1-yl-phenylamine (0.208 g, 0.65 mmol, 91%) as white solid:
 LCMS m/z (%) = 321 ($MH^+ ^{79}Br$, 90), 323 ($MH^+ ^{81}Br$, 100). 1H NMR (400 MHz, $CDCl_3$) δ :
 7.50 (s, 1H), 6.00 (t, J = 1.6 Hz, 1H), 5.99 (t, J = 1.8 Hz, 1H), 5.97 (t, J = 2.0 Hz, 1H), 3.83 (s,
 3H), 3.71 (broad s, 2H), 3.28 (t, J = 6.7 Hz, 4H), 2.00 (dt, J = 3.3, 6.8 Hz, 4H).

Example 9

Synthesis of Compound 70 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenyl]-(4-chloro-phenyl)-amine (Scheme 4):



Scheme 4

Compound **70** was prepared in an analogous method as described by **Method A** using 4-chlorophenylboronic acid and 3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenylamine in 41% yield: LCMS m/z (%) = 392 ($MH^+ ^{79}Br$, 75), 394 ($MH^+ ^{81}Br$, 100). 1H NMR (400 MHz, d_6 -acetone) δ : 7.48 (s, 1H), 7.45 (s, 1H), 7.28 (dd, J = 2.8, 8.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 2.8 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 3H).

Intermediate 3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenylamine was prepared by the following steps:

1) Trifluoro-methanesulfonic acid 2-methoxy-5-nitro-phenyl ester:

To a stirred solution of 2-methoxy-5-nitrophenol (5.092 g, 0.03 mmol) in a mixture of CH_2Cl_2 (3 mL) and pyridine (20 mL) was added triflic anhydride (16.478 g, 9.8 mL, 2.0 eq.) dropwise at 0°C. The mixture was warmed up to r.t. and stirred for 2 hrs. Most of the pyridine was removed under vacuum, the residue was diluted with EtOAc, washed with 1N HCl and water, the aqueous phase was then extracted with EtOAc (3×100 mL). The combined organic

phase was washed with brine, dried over anhydrous MgSO_4 , filtered and evaporated. The crude reaction mixture was purified by SiO_2 column chromatography (Eluent: EtOAc/Hexane = 1/3 then 1/2) to give trifluoro-methanesulfonic acid 2-methoxy-5-nitro-phenyl ester (8.943 g, 0.03 mmol, 100%) as yellow solid: LCMS m/z (%) = 302 (MH^+ , 100). ^1H NMR (400 MHz, CDCl_3) δ : 8.30 (dd, J = 4.0, 8.0 Hz, 1H), 8.16 (d, J = 4.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 4.06 (s, 3H).

2) 5-(2-Methoxy-5-nitro-phenyl)-1-methyl-1H-pyrazole

Trifluoro-methanesulfonic acid 2-methoxy-5-nitro-phenyl ester (2.561 g, 8.50 mmol), 2-methyl-2H-pyrazole-3-boronic acid (4.283 g, 34.01 mmol, 4.0 eq.) and Na_2CO_3 (10.816 g, 102.04 mmol, 12.0 eq.) were dissolved in a mixture of THF (200 mL) and H_2O (100 mL). The mixture was degassed with N_2 for 5 mins, followed by addition of $\text{Pd}(\text{PPh}_3)_4$ (0.486 g, 0.42 mmol, 0.05 eq.). After degassing for another 5 mins it was stirred under Ar at 70°C overnight. Once the reaction was complete, THF was removed and the aqueous phase was extracted with EtOAc (4 \times 100 mL). The combined organic phase was dried over anhydrous MgSO_4 , filtered and evaporated. The crude reaction mixture was purified by SiO_2 column chromatography (Eluent: EtOAc/Hexane = 1/1) to afford compound 5-(2-methoxy-5-nitro-phenyl)-1-methyl-1H-pyrazole (1.799 g, 7.71 mmol, 91%) as white solid: LCMS m/z (%) = 234 (MH^+ , 100). ^1H NMR (400 MHz, CDCl_3) δ : 8.34 (dd, J = 2.8, 9.2 Hz, 1H), 8.19 (d, J = 2.8 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 9.2 Hz, 1H), 6.31 (d, J = 1.6 Hz, 1H), 3.96 (s, 3H), 3.74 (s, 3H).

3) 4-Bromo-5-(2-methoxy-5-nitro-phenyl)-1-methyl-1H-pyrazole:

To a stirred solution of 5-(2-methoxy-5-nitro-phenyl)-1-methyl-1H-pyrazole (1.787 g, 7.66 mmol) in DMF (20 mL) was added NBS (1.515 g, 8.43 mmol, 1.1 eq.) in DMF (5 mL) dropwise at 0°C . Stirring at 0°C for 3 hrs and TLC showed the completion of the reaction. It was diluted with EtOAc (300 mL), washed with water (3 \times 10 mL) and brine. The EtOAc phase was dried over anhydrous MgSO_4 , filtered and evaporated. The crude reaction mixture was purified by SiO_2 column chromatography (Eluent: EtOAc/Hexane = 1/3 then 1/1) to give the product 4-bromo-5-(2-methoxy-5-nitro-phenyl)-1-methyl-1H-pyrazole (2.214 g, 7.09 mmol, 93%) as light yellow solid: LCMS m/z (%) = 312 (MH^+ ^{79}Br , 100), 314 (MH^+ ^{81}Br , 100). ^1H NMR (400 MHz, CDCl_3) δ : 8.40 (dd, J = 2.4, 6.9 Hz, 1H), 8.22 (m, 1H), 7.57 (s, 1H), 7.14 (d, J = 9.2 Hz, 1H), 3.98 (s, 3H), 3.74 (s, 3H).

4) 3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenylamine:

To a stirred solution of 4-bromo-5-(2-methoxy-5-nitro-phenyl)-1-methyl-1H-pyrazole (1.799 g, 5.76 mmol) in EtOH (20 mL) was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (5.306 g, 23.05 mmol, 4.0 eq.), the mixture was stirred at reflux for 2 hrs, and EtOH was removed under vacuum. The resultant solid was dissolved in EtOAc, 1N NaOH (30 mL) was added, and the mixture was

stirred overnight. The white precipitate was filtered off through celite, and the aqueous phase was extracted with EtOAc (3×80 mL). The combined organic phase was dried over anhydrous MgSO₄, filtered and evaporated. The crude reaction mixture was purified by SiO₂ column chromatography (Eluent: EtOAc/Hexane = 1/3 then 1/1) to give 3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenylamine (1.430 g, 5.07 mmol, 88%) as white solid: LCMS m/z (%) = 282 (MH⁺ ⁷⁹Br, 98), 284 (MH⁺ ⁸¹Br, 100). ¹H NMR (400 MHz, CDCl₃) δ: 7.52 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.80 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.22 (d, *J* = 2.4 Hz, 1H), 4.25 (broad s, 2H), 3.72 (s, 3H), 3.71 (s, 3H).

EXAMPLE 10

Intracellular IP₃ Accumulation Assay:

It is well established that human 5-HT_{2A} receptors coupled to the guanine nucleotide binding protein Gq. 5-HT_{2A}-mediated activation of Gq results in activation of membrane associated phospholipase C which in turn catalyzes the hydrolysis of phosphatidylinositol species (PI, PIP, and PIP₂) to form inositol phosphate species (IP, IP₂, and IP₃). The accumulation of inositol phosphate species can be measured and is often used to determine the functional potency of 5-HT_{2A} agonists or antagonists. However, to evaluate compounds for potential inverse agonist activity, the 5-HT_{2A} receptor must display constitutive activity. We have mutated the human 5-HT_{2A} receptor so as to generate a non-endogenous, constitutively activated version of the 5-HT_{2A} receptor, as disclosed in SEQ ID NO:30 (polynucleotide) and SEQ ID NO:31 (polypeptide) in US Patent No. 6,541,209 (the disclosure of which is hereby incorporated by reference in its entirety). Upon transfection of this mutated 5-HT_{2A} into HEK293 cells, it was observed that there was a ligand-independent increase in basal inositol phosphate accumulation compared to untransfected cells. This ligand-independent inositol phosphate accumulation is a trademark of constitutive activity. The following protocol was used to assess inverse agonist potency of compounds.

On day one, 13×10⁶ HEK293 cells per 150 mm plate were plated out. On day two, 2 ml of serum OptimemI is added per plate followed by addition of 60ul of lipofectamine and 16ug of cDNA. Note that lipofectamine must be added to the OptimemI and mixed well before addition of cDNA. While complexes between lipofectamine and the cDNA are forming, media is carefully aspirated and cells are gently rinsed with 5ml of OptimemI media followed by careful aspiration. Then 12 ml of OptimemI is added to each plate and 2 ml of transfection solution is added followed by a 5 hour incubation at 37°C in a 5% CO₂ incubator. Plates are then carefully aspirated and 25 ml of Complete Media are added to each plate and cells are then incubated until used. On day 3, cells are trypsinized with 5 ml of 0.05% trypsin for 20-30 seconds followed by

addition of 10 ml of warmed media, gently titrated to dissociate cells, and then 13 additional ml of warmed media is gently added. Cells are then counted and then 55,000 cells are added to 96-well sterile poly-D-lysine coated plates. Cells are allowed to attach over a six hour incubation at 37°C in a 5% CO₂ incubator. Media is then carefully aspirated and 100 ul of warm inositol-free media plus 0.5 µCi ³H-inositol is added to each well and the plates are incubated for 18-20 hours at 37°C in a 5% CO₂ incubator.

On day 4, media is carefully aspirated and then 0.1 ml of assay medium is added containing inositol-free/serum free media, 10 µM pargyline, 10 mM lithium chloride, and test compound at indicated concentrations. The plates were then incubated for three hours at 37°C and then wells are carefully aspirated. Then 200 ul of ice-cold 0.1M formic acid is added to each well. Plates can then be frozen at this point at -80°C until further processed. Frozen plates are then thawed over the course of one hour, and the contents of the wells (approximately 220ul) are placed over 400ul of washed ion-exchange resin (AG 1-X8) contained in a Multi Screen Filtration plate and incubated for 10 minutes followed by filtration under vacuum pressure. Resin is then washed nine times with 200ul of water and then [³H]inositol phosphates are eluted into a collecting plate by the addition of 200ul of 1M ammonium formate and an additional 5 minute incubation. The elutant is then transferred to 20 ml scintillation vials, 8 ml of SuperMix or Hi-Safe scintillation cocktails is added, and vials are counted for 0.5-1 minutes in a Wallac 1414 scintillation counter.

Inverse agonist IC₅₀ values (the concentration of test compound that inhibits the constitutive inositol phosphate accumulation by 50%) were determined in the human CART 5-HT2A inositol phosphate assay by testing the test compound at 7-8 different concentrations typically ranging from 0.01nM to 10uM. At each concentration, triplicate determinations were made. The mean value of inositol phosphate accumulation at each test compound concentration is calculated and then the data are fit to a non-linear curve-fitting program that allows calculation of the IC₅₀ value.

Example 11

Activity For The Compounds Of The Present Invention in the IP Accumulation

Assay:

Certain compounds of the present invention and their corresponding activities in the IP Accumulation Assay are shown in TABLE 5.

TABLE 5

Compound No.	5-HT _{2A} (IC ₅₀)*
	IP Accumulation Assay (nM)
8	44.6
36	7.00
44	2.99
46	113
49	19.0
57	10.55
70	1.77

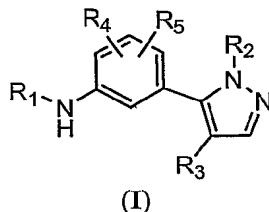
* Reported values are averages of at least two trials.

The majority of the other compounds of the Examples were tested at least once, and they showed activities in the 5-HT_{2A} IP Accumulation Assay in the range between about 4 nM and about 10 μ M.

CLAIMS

We claim:

1. A compound of Formula (I):



wherein:

- i) R_1 is aryl or heteroaryl optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-6} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide, C_{2-8} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl, thiol, nitro, phenoxy and phenyl; and wherein C_{2-6} alkenyl, C_{1-6} alkyl and C_{2-6} alkynyl substituents may be optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-6} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl, thiol and nitro; or two adjacent substituents together with the ring carbons to which they are bonded form a C_{5-7} cycloalkyl optionally replaced with 1 to 2 oxygen atoms;
- ii) R_2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{3-7} cycloalkyl;
- iii) R_3 is H, C_{2-6} alkenyl, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylcarboxamide, halogen, heteroaryl or phenyl; and

wherein C₂₋₆ alkenyl, C₁₋₆ alkyl, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₃₋₇ cycloalkyl, heteroaryl or phenyl may be optionally substituted with 1 to 5 substituents selected independently from the group consisting of C₂₋₆ alkenyl, C₁₋₆ alkyl, C₁₋₄ alkoxy, amino, C₁₋₄ alkylamino, C₂₋₆ alkynyl, C₂₋₈ dialkylamino, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, hydroxyl and thiol; and

iv) R₄ and R₅ are independently H, C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₆ alkyl, C₁₋₅ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylthio, C₁₋₆ alkylureyl, carbo-C₁₋₆-alkoxy, carboxamide, carboxy, cyano, C₃₋₇ cycloalkyl, C₂₋₈ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, hydroxyl, thiol, 5 or 6 membered-heteroaryl, nitro, phenyl or NR₆R₇, and where the 5 or 6 membered-heteroaryl or phenyl is optionally substituted with a substituents selected from the group consisting of H, C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₆ alkyl, C₁₋₅ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylthio, C₁₋₆ alkylureyl, carbo-C₁₋₆-alkoxy, carboxamide, carboxy, cyano, C₃₋₇ cycloalkyl, C₂₋₈ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, hydroxyl, thiol and nitro;

wherein:

R₆ and R₇ are independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl, phenyl and benzyl group; wherein each said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl, phenyl and benzyl group is optionally substituted with 1 to 5 substituents selected independently from the group consisting of H, C₁₋₅ acyl, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₆ alkyl, C₁₋₅ alkylcarboxamide, C₁₋₄ alkylthio, carbo-C₁₋₆-alkoxy, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, carboxamide, carboxy, cyano, C₃₋₇ cycloalkyl, C₂₋₈ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, hydroxyl, thiol and nitro; or

R₆ and R₇ together with the nitrogen to which they are bonded form a 5, 6 or 7 membered cyclic structure which can be saturated or unsaturated and can contain up to four heteroatoms selected from O, NR₈ or S and said cyclic structure may be optionally substituted with 1 to 5 substituents selected independently from the group consisting of H, C₁₋₅ acyl, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₆ alkyl, C₁₋₅ alkylcarboxamide, C₁₋₄ alkylthio, carbo-C₁₋₆-alkoxy, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, carboxamide, carboxy, cyano, C₃₋₇ cycloalkyl, C₂₋₈ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, hydroxyl, thiol and nitro;

R₈ is H or C₁₋₆ alkyl;

or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

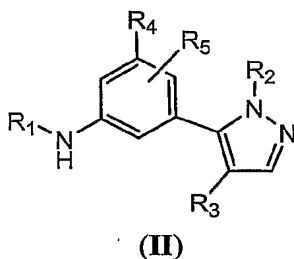
2. The compound according to claim 1 wherein R₁ is aryl optionally substituted with 1 to 5 substituents selected independently from the group consisting of C₁₋₅ acyl, C₁₋₄ alkoxy, C₁₋₆ alkyl, C₁₋₅ alkylcarboxamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylthio, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, carboxamide, carboxy, carbo-C₁₋₆-alkoxy, cyano, C₂₋₈ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, hydroxyl, thiol, nitro and phenoxy; and where C₁₋₆ alkyl is optionally substituted with 1 to 3 substituents selected from the group consisting of C₁₋₄ alkoxy, C₁₋₅ alkylcarboxamide, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, hydroxyl and thiol.
3. The compound according to claim 2 wherein R₁ is aryl optionally substituted with 1 to 5 substituents selected independently from the group consisting of NO₂, F, Cl, Br, I, CF₃, CF₂CF₃, OCH₃, OCH₂CH₃, OCF₃, OCF₂CF₃, SCH₃, SCH₂CH₃, S(O)CH₃, S(O)CH₂CH₃, S(O)₂CH₃, S(O)₂CH₂CH₃, CO₂H, CN, COCH₃, COCH₂CH₃, CH₃, CH₂CH₃, NHCOCH₃, CH₂OH and OC₆H₅.
4. The compound according to claim 3 wherein R₁ is aryl optionally substituted with 1 to 3 substituents selected independently from the group consisting of NO₂, F, Cl, Br, I, CF₃, OCH₃, OCF₃, SCH₃, S(O)CH₃, S(O)₂CH₃, CN, COCH₃, CH₃, CH₂OH and OC₆H₅.

5. The compound according to claim 4 wherein R₁ is aryl optionally substituted with 1 to 3 substituents selected independently from the group consisting of NO₂, F, Cl, Br, I, CF₃, OCH₃, OCF₃, SCH₃, S(O)CH₃, S(O)₂CH₃, CN and CH₃.
6. The compound according to claim 5 wherein R₁ is aryl optionally substituted with 1 to 3 substituents selected independently from the group consisting of F, Cl, Br, I, CF₃, OCH₃ and OCF₃.
7. The compound according to claim 6 wherein the aryl group is phenyl substituted with 1 to 3 substituents selected independently from the group consisting of F, Cl and CF₃.
8. The compound according to claim 6 wherein the aryl group is 2-naphthyl substituted with 1 to 3 substituents selected independently from the group consisting of F, Cl and CF₃.
9. The compound according to claim 1 wherein R₁ is aryl and two adjacent substituents together with the ring carbons to which they are bonded form a C₅₋₇ cycloalkyl optionally replaced with 1 to 2 oxygen atoms.
10. The compound according to claim 9 wherein R₁ is a 3,4-methylenedioxyphenyl or 3,4-ethylenedioxyphenyl group.
11. The compound according to claim 1 wherein R₁ is heteroaryl and is optionally substituted with 1 to 5 substituents selected independently from the group consisting of C₁₋₅ acyl, C₁₋₄ alkoxy, C₁₋₆ alkyl, C₁₋₅ alkylcarboxamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylthio, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, carboxamide, carboxy, carbo-C₁₋₆-alkoxy, cyano, C₂₋₈ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, hydroxyl, thiol, nitro and phenoxy; and where C₁₋₆ alkyl is optionally substituted with 1 to 3 substituents selected from the group consisting of C₁₋₄ alkoxy, C₁₋₅ alkylcarboxamide, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, hydroxyl and thiol.
12. The compound according to claim 11 wherein R₁ is heteroaryl and is optionally substituted with 1 to 3 substituents selected independently from the group consisting

of C₁₋₄ alkoxy, C₁₋₆ alkyl, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, carbo-C₁₋₆-alkoxy, carboxamide, carboxy, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, hydroxyl, thiol and nitro.

13. The compound according to claim 12 wherein the heteroaryl is selected from the group consisting of quinolinyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, quinazolinyl and pyrimidinyl.
14. The compound according to claim 13 wherein the heteroaryl is selected from the group consisting of benzoxazol-2-yl, quinolin-2-yl, quinolin-3-yl benzimidazol-2-yl, and benzothiazol-2-yl.
15. The compound according to any one of claims 1 to 15 wherein R₂ is C₁₋₆ alkyl.
16. The compound according to claim 15 wherein R₂ is CH₃, CH₂CH₃, CH(CH₃)₂ or CH₂CH₂CH₃.
17. The compound according to claim 16 wherein R₂ is CH₃.
18. The compound according to any one of claims 1 to 17 wherein R₃ is H, C₂₋₆ alkenyl, C₁₋₆ alkyl, C₂₋₆ alkynyl, carbo-C₁₋₆-alkoxy, carboxamide, carboxy, cyano, C₃₋₇ cycloalkyl, halogen, 5 membered-heteroaryl or phenyl; and where C₂₋₆ alkenyl, C₁₋₆ alkyl or phenyl group may be optionally substituted with 1 to 3 substituents selected independently from the group consisting of C₁₋₄ alkoxy, C₂₋₆ alkynyl, C₂₋₈ dialkylamino, halogen, C₁₋₄ haloalkoxy and hydroxyl.
19. The compound according to claim 18 wherein R₃ is H, Cl, Br, CO₂CH₃, CO₂CH₂CH₃, 2-hydroxyethyl, 2-dimethylaminoethyl, 2-diethylaminoethyl, vinyl, CH₃, CH₂CH₃, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, CO₂H, cyclopropyl, -CCH, -CH=CH-CCH or CN.
20. The compound according to claim 19 wherein R₃ is H, Cl or Br.

21. The compound according to any one of claims 1 to 20 wherein R_4 is H, halogen or NR_6R_7 .
22. The compound according to claim 21 wherein R_4 is H, F, $N(CH_3)_2$, or pyrrolidin-1-yl.
23. The compound according to any one of claims 1 to 22 wherein R_5 is H.
24. The compound according to any one of claims 1 to 20 having Formula (II):



wherein:

R_4 is H, C_{1-4} alkoxy, phenyl, halogen, 5 or 6 membered-heteroaryl, hydroxyl, thiol or NR_6R_7 , where the phenyl or heteroaryl group is optionally substituted with 1 to 5 substituents independently selected from the group consisting of C_{1-5} acyl, C_{1-4} alkoxy, C_{1-6} alkyl, C_{1-5} alkylcarboxamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, cyano, C_{2-8} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, thiol and nitro; and

wherein:

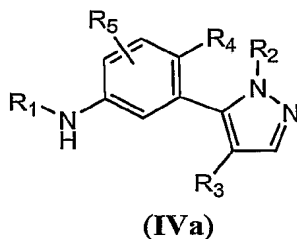
R_6 and R_7 are independently H, C_{1-6} alkyl, or

R_6 and R_7 together with the nitrogen to which they are bonded form a 5, 6 or 7 membered cyclic structure that may contain up to four heteroatoms selected from O, S or N- C_{1-4} alkyl; and

R_5 is H, C_{1-4} alkoxy, C_{1-6} alkyl, carboxamide, carboxy, cyano, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, thiol or nitro.

25. The compound according to claim 24 wherein R_4 is H, Cl, F, dimethylamino, diethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, hydroxyl, thiol, OCH_3 or OCH_2CH_3 .
26. The compound according to claim 24 or 25 wherein R_5 is H or halogen.

27. The compound according to any one of claims 1 to 20 having Formula (IVa):



wherein:

R₄ is H, or C₁₋₄ alkoxy; and

R₅ is H, C₁₋₄ alkoxy, C₁₋₆ alkyl, carboxamide, carboxy, cyano, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, hydroxyl, thiol or nitro.

28. The compound according to claim 27 wherein R₄ is OCH₃.
29. The compound according to claim 28 wherein R₅ is H.
30. The compound according to claim 1 selected from the group consisting of:
 (4-Chloro-phenyl)-[3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-amine;
 [3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethyl-phenyl)-amine;
 [3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethoxy-phenyl)-amine;
 [3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-(3-trifluoromethoxy-phenyl)-amine;
 [3-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-(4-fluoro-phenyl)-amine;
 (4-Chloro-phenyl)-[4-methoxy-3-(2-methyl-2H-pyrazol-3-yl)-phenyl]-amine;
 (4-Chloro-phenyl)-[3-(2-isopropyl-2H-pyrazol-3-yl)-phenyl]-amine
 and
 (4-Fluoro-phenyl)-[3-(2-isopropyl-2H-pyrazol-3-yl)-phenyl]-amine.
31. The compound according to claim 1 selected from the group consisting of:
 [3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-chloro-phenyl)-amine;
 [3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethyl-phenyl)-amine;
 [3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethoxy-phenyl)-amine;

[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-trifluoromethoxy-phenyl)-amine

and

[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-fluoro-phenyl)-amine.

32. The compound according to claim 1 selected from the group consisting of:

[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-methyl-4-chloro-phenyl)-amine;

[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-chloro-4-trifluoromethyl-phenyl)-amine;

[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,4-difluoro-phenyl)-amine;

[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-chloro-phenyl)-amine;

[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-methoxy-phenyl)-amine;

[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenyl]-(4-chloro-phenyl)-amine;

(4-Chloro-phenyl)-[3-(4-fluoro-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenyl]-amine;

and

(4-Chloro-phenyl)-[3-(4-fluoro-2-methyl-2H-pyrazol-3-yl)-phenyl]-amine.

33. The compound according to claim 1 selected from the group consisting of:

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2-nitro-phenyl)-amine;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-chloro-phenyl)-amine;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,5-bis-trifluoromethyl-phenyl)-amine;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-methoxy-phenyl)-amine;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,4-dimethoxy-phenyl)-amine;

1-{3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamino]-phenyl}-ethanone;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,5-dichloro-phenyl)-amine;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,5-dimethyl-phenyl)-amine;

N-{3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamino]-phenyl}-
 acetamide;
 {3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamino]-phenyl}-
 methanol;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2-methyl-4-chloro-
 phenyl)-amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-phenoxy-phenyl)-amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-trifluoromethyl-phenyl)-
 amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-nitro-phenyl)-amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2,3,4-trimethoxy-phenyl)-
 amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-fluoro-4-methyl-phenyl)-
 amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2,4-bis-trifluoromethyl-
 phenyl)-amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-fluoro-4-methoxy-
 phenyl)-amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2,3-difluoro-phenyl)-
 amine
 and
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2,4-difluoro-phenyl)-
 amine.

34. The compound according to claim 1 selected from the group consisting of:

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-chloro-phenyl)-amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-fluoro-phenyl)-amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-methoxy-phenyl)-amine;
 Benzo[1,3]dioxol-5-yl-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-
 amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-trifluoromethoxy-
 phenyl)-amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-bromo-phenyl)-amine;
 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-methylsulfanyl-phenyl)-
 amine;

4-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamino]-benzonitrile;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethyl-phenyl)-
amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethoxy-
phenyl)-amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-methanesulfonyl-
phenyl)-amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-chloro-4-fluoro-phenyl)-
amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,4-dichloro-phenyl)-
amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-methyl-4-chloro-
phenyl)-amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,5-difluoro-phenyl)-
amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-chloro-4-
trifluoromethyl-phenyl)-amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,4-difluoro-phenyl)-
amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-methyl-4-fluoro-phenyl)-
amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2-methyl-4-fluoro-phenyl)-
amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-iodo-phenyl)-amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(2-methoxy-5-methyl-
phenyl)-amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(*N,N*-dimethylamino)-phenyl]-(4-
chloro-phenyl)-amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-(4-chloro-phenyl)-
amine;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-(4-chloro-
phenyl)-amine and
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenyl]-(4-chloro-
phenyl)-amine.

35. The compound according to claim 1 selected from the group consisting of:
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-chloro-phenyl)-amine;
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-fluoro-phenyl)-amine;
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-trifluoromethoxy-phenyl)-amine;
 - 4-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenylamino]-benzonitrile;
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethyl-phenyl)-amine;
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(4-trifluoromethoxy-phenyl)-amine;
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3-methyl-4-chloro-phenyl)-amine;
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(3,4-difluoro-phenyl)-amine;
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4-methoxy-phenyl]-(4-chloro-phenyl)-amine;
 - [3-(4-Bromo-2-isopropyl-2H-pyrazol-3-yl)-phenyl]-(4-fluoro-phenyl)-amine;
 - and
 - [3-(4-Bromo-2-isopropyl-2H-pyrazol-3-yl)-phenyl]-(4-chloro-phenyl)-amine.
36. The compound according to claim 1 selected from the group consisting of:
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-naphthalen-1-yl-amine and
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-naphthalen-2-yl-amine.
37. The compound according to claim 1 selected from the group consisting of:
- Benzoxazol-2-yl-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-amine;
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-quinolin-2-yl-amine;
 - (1H-Benzoimidazol-2-yl)-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-amine;
 - Benzothiazol-2-yl-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-amine;
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(5-methoxy-benzothiazol-2-yl)-amine;
 - [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-quinolin-3-yl-amine
 - and

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-(5-chloro-benzothiazol-2-yl)-amine.

38. A pharmaceutical composition comprising a compound according to any one of claims 1 to 37 and a pharmaceutically acceptable carrier.
39. A method for modulating the activity of a human 5HT_{2A} serotonin receptor comprising contacting the receptor with a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
40. A method for prophylaxis or treatment of reducing platelet aggregation in an individual comprising administering to said individual in need of such prophylaxis or treatment a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
41. A method for prophylaxis or treatment of an indication selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation in an individual comprising administering to said individual in need of said treatment or prophylaxis a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
42. A method for prophylaxis or treatment of reducing a risk of blood clot formation in an angioplasty or coronary bypass surgery individual, comprising administering to said individual in need of such prophylaxis or treatment a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
43. A method for prophylaxis or treatment of reducing risk of blood clot formation in an individual suffering from atrial fibrillation, comprising administering to said individual in need of such prophylaxis or treatment a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
44. A method for prophylaxis or treatment of asthma in an individual, comprising administering to said individual in need of such prophylaxis or treatment a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.

45. A method for the prophylaxis or treatment of a symptom of asthma in an individual, comprising administering to said individual in need of such prophylaxis or treatment a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
46. A method for the prophylaxis or treatment of agitation or a symptom thereof in an individual, comprising administering to said individual in need of such prophylaxis or treatment a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
47. The method according to claim 46 wherein said individual is a cognitively intact elderly individual.
48. A method for prophylaxis or treatment of agitation or a symptom thereof in an individual suffering from dementia, comprising administering to said individual in need of such prophylaxis or treatment a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
49. The method according to claim 48 wherein said dementia is due to a degenerative disease of the nervous system.
50. The method according to claim 49 wherein said dementia is Alzheimers disease, Lewy Body, Parkinson's disease, or Huntington's disease.
51. The method according to claim 48 wherein said dementia is due to diseases that affect blood vessels.
52. The method according to claim 48 wherein said dementia is due to stroke or multi-infarct dementia.
53. A method for prophylaxis or treatment of an individual suffering from at least one of the indications selected from the group consisting of behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute

schizophrenia, chronic schizophrenia and NOS schizophrenia comprising administering to said individual in need of such prophylaxis or treatment a dopamine D2 receptor antagonist and a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.

54. The method of claim 53 wherein said dopamine D2 receptor antagonist is haloperidol.
55. A method for prophylaxis or treatment of an individual with infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to said individual in need of such prophylaxis or treatment a dopamine D2 receptor antagonist and a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
56. The method according to claim 55 wherein said dopamine D2 receptor antagonist is haloperidol.
57. A method for prophylaxis or treatment of schizophrenia in an individual, comprising administering to said individual in need of such prophylaxis or treatment a dopamine D2 receptor antagonist and a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
58. The method of claim 57 wherein said dopamine D2 receptor antagonist is haloperidol.
59. A method for prophylaxis or treatment of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to an individual suffering from said schizophrenia, comprising administering to said individual in need of such prophylaxis or treatment a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
60. The method according to any one of claims 54, 56, 58 and 59 wherein said haloperidol and said compound or pharmaceutical composition are administered in separate dosage forms.

61. The method according to any one of claims 54, 56, 58 and 59 wherein said haloperidol and said compound or pharmaceutical composition are administered in a single dosage form.
62. A method for prophylaxis or treatment of a sleep disorder in an individual comprising administering to said individual in need of such prophylaxis or treatment a compound according to any one of claims 1 to 37 or a pharmaceutical composition according to claim 38.
63. A compound according to any one of claims 1 to 37 for use in a method of treatment of the human or animal body by therapy.
64. A compound according to any one of claims 1 to 37 for use in a method for the prophylaxis or treatment of reducing platelet aggregation in the human or animal body by therapy.
65. A compound according to any one of claims 1 to 37 for use in a method for the prophylaxis or treatment of an indication selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation in the human or animal body by therapy.
66. A compound according to any one of claims 1 to 37 for use in a method for the prophylaxis or treatment of reducing risk of blood clot formation in an angioplasty or coronary bypass surgery in the human or animal body by therapy.
67. A compound according to any one of claims 1 to 37 for use in a method for the prophylaxis or treatment of reducing risk of blood clot formation in the human or animal body by therapy.
68. A compound according to any one of claims 1 to 37 for use in a method for the prophylaxis or treatment of asthma in the human or animal body by therapy.
69. A compound according to any one of claims 1 to 37 for use in a method for the prophylaxis or treatment of a symptom of asthma in the human or animal body by therapy.

70. A compound according to any one of claims 1 to 37 for use in a method for the prophylaxis or treatment of agitation or a symptom thereof in the human or animal body by therapy.
71. A compound according to any one of claims 1 to 37 for use in a method for the prophylaxis or treatment of at least one of the indications selected from the group consisting of behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia in the human or animal body by therapy.
72. A compound according to any one of claims 1 to 37 for use in a method for the prophylaxis or treatment of a sleep disorder in the human or animal body by therapy.
73. Use of a compound according to any one of claims 1 to 37 for production of a medicament for use in prophylaxis or treatment of a 5HT_{2A} mediated disorder.
74. The use according to claim 73 wherein the disorder is platelet aggregation.
75. The use according to claim 73 wherein the disorder is selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation.
76. The use according to claim 73 wherein the disorder is a blood clot formation in an angioplasty or coronary bypass surgery individual.
77. The use according to claim 73 wherein the disorder is a blood clot formation in an individual suffering from atrial fibrillation.
78. The use according to claim 73 wherein the disorder is asthma.
79. The use according to claim 73 wherein the disorder is a symptom of asthma.

80. The use according to claim 73 wherein the disorder is agitation or a symptom thereof in an individual.
81. The use according to claim 80 wherein the individual is a cognitively intact elderly individual.
82. The use according to claim 73 wherein the disorder is agitation or a symptom thereof in an individual suffering from dementia.
83. The use according to claim 82 wherein the dementia is due to a degenerative disease of the nervous system.
84. The use according to claim 83 wherein the dementia is Alzheimers disease, Lewy Body, Parkinson's disease, or Huntington's disease.
85. The use according to claim 82 wherein the dementia is due to diseases that affect blood vessels.
86. The use according to claim 82 wherein the dementia is due to stroke or multi-infract dementia.
87. The use according to claim 73 further comprising a dopamine D2 receptor antagonist wherein the disorder is selected from the group consisting of a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia.
88. The use according to claim 87 wherein said dopamine D2 receptor antagonist is haloperidol.
89. The use according to claim 73 further comprising a dopamine D2 receptor antagonist wherein the disorder is infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/40844

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/12 A61K31/415 A61P7/02 C07D405/12 C07D413/12
C07D401/12 C07D403/12 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 140 509 A (SMITH JULIAN R ET AL) 31 October 2000 (2000-10-31) column 34; claim 1 -----	1-97

☐

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

° Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

5 April 2004

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/40844

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 39-62 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/40844

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6140509	A	31-10-2000	
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		ES 2156845 T1	01-08-2001
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		US 6426541 B1	16-07-2002
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		US 2003224442 A1	04-12-2003

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- (21) International Application Number: PCT/US2004/003411 (74) Agents: **WARBURG, Richard** et al.; FOLEY & LARDNER, P.O. Box 80278, San Diego, CA 92138-0278 (US).
- (22) International Filing Date: 6 February 2004 (06.02.2004) (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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- (71) Applicant (for all designated States except US): **KEMIA INC.** [US/US]; 5871 Oberlin Drive, Suite 100, San Diego, CA 92121 (US).
- (72) Inventors; and
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS FOR THE TREATMENT OF VIRAL INFECTION

(57) Abstract: The present invention is related to compounds, their intermediates, processes for their preparation and use, and pharmaceutical compositions comprising the compounds. The novel compounds are useful in therapy, and in particular for the treatment of viral infection, particularly HIV infection.

WO 2004/071426 A2

Compounds for the Treatment of Viral Infection

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to the U.S. Provisional Application 60/513,217, filed November 18, 2003 and claims priority to U.S. Provisional Application 60/446,713, filed February 11, 2003, the entire contents of which are incorporated herein by reference and for all purposes.

FIELD OF THE INVENTION

[0002] The present invention is related to compounds, intermediates and methods for the preparation and use thereof, and pharmaceutical compositions comprising the compounds. The novel compounds are useful in antiviral therapy, and in particular for the treatment of HIV infection.

BACKGROUND OF THE INVENTION

[0003] HIV, human immunodeficiency virus, causes acquired immunodeficiency syndrome (AIDS) and while recent advances in drug therapies have been successful in slowing the progression of AIDS, there is still a need to find a safer, more efficient and less expensive way to control this and other viruses. One approach for the development of anti-virals is to inhibit the entry of the virus, such as HIV, into cells. Such an approach should be widely applicable to other viruses, including influenza human respiratory syncytial virus (HRSV), and ebola virus.

[0004] For example, the recent elucidation of the HIV entry process has identified many new protein targets for intervention. The function of such proteins is to induce structural changes that allow viral fusion to take place. HIV is an enveloped virus that enters cells by a two step procedure that involves first recognition of receptors on a host cell and then fusion of the viral and host cell membranes. Both of these steps are governed by the envelope protein complex. This complex initially exists as the precursor protein gp160, which is heavily glycosylated and then cleaved by cellular convertase into two subunits: the surface subunit gp120 and the transmembrane subunit gp41. The protein

gp41 controls the fusion mechanism of the virus and is activated by gp120 recognition of CD4 receptors and subsequent association of gp120 and a chemokine coreceptor.

[0005] Analysis of the entry mechanism of HIV reveals that inhibition of the formation of a critical hexameric helical bundle conformation of gp41 should halt the fusion process. [a) "Peptide and Non-Peptide HIV Fusion Inhibitors," S. Jiang, Q. Zhao, A. K. Debnath *Curr. Pharm. Design* **2002**, 8, 125-133; b) "HIV-1 Membrane Fusion: Targets of Opportunity," R. W. Doms, J. P. Moore *J. Cell Biol.* **2000**, 151, F9-F13; c) HIV Fusion and Its Inhibition," C. C. LaBranche, G. Galasso, J. P. Moore, D. P. Bolognesi, M. S. Hirsch, S. M. Hammer *Antiviral Res.* **2001**, 90, 95-115; d) "HIV-1 Entry – An Expanding Portal for Drug Discovery," W. S. Blair, P-F. Lin, N. A. Meanwell, O. B. Wallace *Drug Discovery Today* **2000**, 5, 183-194; e) "Development of HIV Entry Inhibitors Targeted to the Coiled-Coil Regions of gp41," S. Jiang, A. K. Debnath *Biochem. Biophys. Res. Commun.* **2000**, 269, 641-646; f) "HIV Entry and Its Inhibition," D. C. Chan, P. S. Kim *Cell* **1998**, 93, 681-684.] The hypothesis of six-helix bundle antagonism has been validated by the fact that peptides with sequences derived from gp41 are potent inhibitors of viral fusion. For example, Wild *et al.* has shown that a peptide, DP-178 (T20), is a potent antiviral agent, with an EC₅₀ of 1 ng/mL in cell culture. ["Peptides Corresponding to a Predictive α -Helical Domain of Human Immunodeficiency Virus Type 1 gp41 are Potent Inhibitors of Virus Infection," C. T. Wild, D. C. Shugars, T. K. Greenwell, C. B. McDanal, T. J. Matthews *Proc. Natl. Acad. Sci. USA* **1994**, 91, 9770-9774.] The T20 peptide (also known as Fuzeon) received FDA approval in March 2003 for the treatment of HIV infected individuals who have shown resistance to currently marketed reverse transcriptase and protease inhibitors. However, T20 and other peptide agents are unsuitable for oral administration and suffer from poor pharmacokinetic properties.

[0006] Other enveloped viral glycoproteins, such as RSV F and Ebola GP2 proteins, show structural and mechanistic similarities to gp41. ["Mechanisms of Viral Membrane Fusion and Its Inhibition", D. M. Eckert and P. S. Kim *Annu. Rev. Biochem.* **2001**, 70, 777-810]. Such proteins constitute additional targets for inhibition of viral entry into cells.

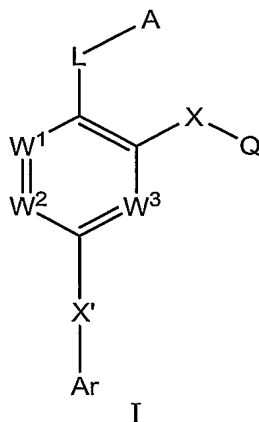
[0007] Therefore a need exists in the art to identify non-peptidic compounds that antagonize the function of gp41 and related proteins and thus inhibit viral entry into cells. In particular, there is a need for non-peptidic compounds that inhibit HIV entry and infection. The compounds having structures outlined below represent a class of molecules that address these needs and possess other advantages.

SUMMARY OF THE INVENTION

[0008] In various aspects, the present invention relates in part to compounds, including those having Formulas I and II; to intermediates of Formula III; to processes for preparing compounds of Formulas I and II; to compositions for treatment using such compounds; to methods of use and treatment with such compounds; and to methods of identifying subjects in need of such treatments.

[0009] Thus, one aspect of the invention provides compounds having a first planar moiety directly or indirectly attached to an acidic moiety, to a hydrophobic planar moiety, and to a second planar moiety bearing one or more non-aryl and non-heteroaryl substituents. The first planar moiety is typically a substituted or unsubstituted 6-member aryl or heteroaryl ring that holds the other moieties in a particular orientation relative to each other. The acidic moiety includes a group with at least one acidic proton, such as a carboxylic acid, a boronic acid, or a tetrazole, or a hydrogen bond donor and/or acceptor such as an amide group. Alternatively, the acidic moiety may include a functionality that may be readily converted *in vivo* or by chemical synthesis to an acidic moiety, e.g. an ester or a primary alcohol. The hydrophobic moiety is typically a large non-polar moiety that may include two or more rings such as phenyl rings and may be substituted or unsubstituted. The second planar moiety may be any of a variety of substituted aryl or heteroaryl rings with one or more non-aryl and non-heteroaryl substituents.

[0010] In another aspect, the invention provides compounds having Formula I:



wherein:

A is hydrogen, OH, NO₂, -COOR, -C(O)NROH, -C(O)CF₃, -B(OH)₂, -SO₃H, -PO₃R₂, -OPO₃R₂, -C(O)NHSO₂R, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, OR, CN, NRR, NO₂, R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR;

L is -(CR⁴R⁵)_m-, -O-(CR⁴R⁵)_m-, -S(O)_q-(CR⁴R⁵)_m-, -NR-(CR⁴R⁵)_m-, -NR-C(O)-(CR⁴R⁵)_m-, -C(O)O-(CR⁴R⁵)_m-, -C(O)NR-(CR⁴R⁵)_m-, -NR-C(O)-O(CR⁴R⁵)_m-, -NR-C(O)NR-(CR⁴R⁵)_m-, -S(O)₂-NR-(CR⁴R⁵)_m-, or -NR-S(O)₂-(CR⁴R⁵)_m-, provided that L and A together are not H, -CH₃, OH, or -OCH₃.

W¹ is N or CR¹;

W² is N or CR²;

W³ is N or CR³;

X is -(CR⁶R⁷)_r-, -O-(CR⁶R⁷)_r-, -S(O)_q-(CR⁶R⁷)_r-, -NR-(CR⁶R⁷)_r-, -NR-C(O)-(CR⁶R⁷)_r-, -C(O)O-(CR⁶R⁷)_r-, -C(O)NR-(CR⁶R⁷)_r-, -NR-C(O)-O(CR⁶R⁷)_r-, -NR-C(O)NR-(CR⁶R⁷)_r-, -S(O)₂-NR-(CR⁶R⁷)_r-, or -NR-S(O)₂-(CR⁶R⁷)_r;

X' is a covalent bond, O, S(O)_q, -NR-, -N(C(O)-R)-, -N(C(O)-OR)-, -N(C(O)-NRR)-, -NR-C(O)-, -NR-C(O)-NR-, substituted or unsubstituted C₁₋₄ alkyl, substituted or unsubstituted C₂ alkenyl, or acetylenyl;

Q is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclalkyl;

Ar is aryl or heterocyclyl, each substituted with one or more R';

R at each occurrence is independently hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted (C₀₋₄ alkylene)(C₆₋₁₀ aryl), or substituted or unsubstituted (C₀₋₄ alkylene)(C₁₋₉ heterocyclyl);

R' at each occurrence is independently, F, Cl, Br, I, NO₂, CN, substituted or unsubstituted C₁₋₈ alkyl, substituted or unsubstituted C₂₋₈ alkenyl, substituted or unsubstituted (C₁₋₆ alkylene)(C₆₋₁₄ aryl), substituted or unsubstituted (C₁₋₆ alkylene)(C₁₋₁₃ heterocyclyl), OR⁸, -C(O)R⁸, -COOR⁸, -S(O)_qR⁸, -NR⁸R⁹, -C(Y)NR⁸R⁹, -N(R⁸)C(Y)OR⁹, -NR¹⁰C(Y)NR⁸R⁹, -NR¹⁰C(NR¹¹)NR⁸R⁹, -C(NR¹⁰)NR⁸R⁹, -NR¹⁰NR⁸R⁹, -NR⁸OR⁹, -S(O)_qNR⁸R⁹, or -NR⁸-SO₂-R⁹, wherein Y is O or S;

R¹, R², and R³, at each occurrence, are independently hydrogen, F, Cl, Br, I, CN, NO₂, substituted or unsubstituted C₁₋₈ alkyl, substituted or unsubstituted C₂₋₈ alkenyl, substituted or unsubstituted (C₀₋₆ alkylene)(C₆₋₁₄ aryl), substituted or unsubstituted (C₀₋₆ alkylene)(C₁₋₁₃ heterocyclyl), OR⁸, -C(O)R⁸, -COOR⁸, -S(O)_qR⁸, -NR⁸R⁹, -C(Y')NR⁸R⁹, -N(R⁸)C(Y')OR⁹, -NR¹⁰C(Y')NR⁸R⁹, -NR¹⁰C(NR¹¹)NR⁸R⁹, -C(NR¹⁰)NR⁸R⁹, -NR¹⁰NR⁸R⁹, -NR⁸OR⁹, -S(O)_qNR⁸R⁹, or -NR⁸-SO₂-R⁹, wherein each Y' is independently O or S;

R⁴ and R⁵ are, at each occurrence, independently hydrogen, F, Cl, Br, I, substituted or unsubstituted straight or branched C₁₋₄ alkyl, substituted or unsubstituted C₂₋₄ alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, -

OR, -COOR -NRR; or R⁴ and R⁵, together with the carbon to which they are attached, form a carbonyl;

R⁶ and R⁷ are, at each occurrence, independently hydrogen, F, Cl, Br, I, substituted or unsubstituted straight or branched C₁₋₄ alkyl, substituted or unsubstituted C₂₋₄ alkenyl, -OR, -COOR -NRR; or when r is 2 or 3, R⁶ and R⁷, together with the carbon to which they are attached, may form a carbonyl;

R⁸, R⁹, R¹⁰, and R¹¹, at each occurrence, are independently hydrogen, substituted or unsubstituted C₁₋₈ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted (C₀₋₆ alkylene)(C₆₋₁₀ aryl), or substituted or unsubstituted (C₀₋₆ alkylene)(C₁₋₉ heterocyclyl); or R⁸ and R⁹, together with the N to which they are attached, form a substituted or unsubstituted heterocyclic ring;

m = 0 - 4;

each q is independently 0 - 2; and

r = 0 - 3;

and stereoisomers thereof, tautomers thereof, solvates thereof, prodrugs thereof, and pharmaceutically acceptable salts thereof.

[0011] In some embodiments, the compounds of Formula I do not include acetic acid 3'-(2-acetoxy-4-methoxy-benzoyl)-5-benzoyl-2-methoxy-biphenyl-4-yl ester, acetic acid 5'-(2-acetoxy-4-methoxy-benzoyl)-2,2'-dimethoxy-5-(4-methoxy-benzoyl)-biphenyl-4-yl ester, 5,5'-bis-[bis-(4-tert-butyl-phenyl)-methoxy-methyl]-2,4,2',4'-tetraisopropyl-biphenyl, 3-acetoxy-5-methyl-2-[2,4,2',4'-tetraacetoxy-3'-(2-methoxycarbonyl-4-methyl-6-acetoxybenzoyl)-biphenyl-3-carbonyl]-benzoic acid methyl ester, 3-(3-benzyl-4'-methoxy-biphenyl-4-yl)-propionic acid, 3-(3-benzyl-4'-methoxy-biphenyl-4-yl)-propionyl chloride, or (4,4'-diamino-3'-benzoyl-biphenyl-3-yl)-phenyl-methanone.

[0012] In some embodiments of compounds having Formula I, A is OH, NO₂, -COOR, -C(O)NROH, -C(O)CF₃, -B(OH)₂, -SO₃H, -PO₃R₂, -OPO₃R₂, -C(O)NH₂SO₂R, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or

pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, OR, CN, NRR, NO₂, R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR. In other embodiments, A is hydrogen, -COOR, -C(O)NROH, -C(O)CF₃, -B(OH)₂, -SO₃H, -PO₃H₂, -OPO₃H₂, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, OR, CN, NRR, NO₂, R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR. In still other embodiments, A is substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, OR, CN, NRR, NO₂, R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR. In yet other embodiments, A is -COOR, -C(O)NHOH, -C(O)CF₃, or -B(OH)₂. In certain embodiments, A is -COOR or -COOH.

[0013] In some embodiments of compounds having Formula I, L is $-(CR^4R^5)_m-$, $-O-(CR^4R^5)_m-$, $-S(O)_q-(CR^4R^5)_m-$, $-NR-(CR^4R^5)_m-$, $-NR-C(O)-(CR^4R^5)_m-$, $-C(O)O-(CR^4R^5)_m-$, $-C(O)NR-(CR^4R^5)_m-$, $-NR-C(O)-O-(CR^4R^5)_m-$, or $-NR-C(O)NR-(CR^4R^5)_m-$. In other embodiments, L is $-(CR^4R^5)_m-$, $-O-(CR^4R^5)_m-$, $-S(O)_q-(CR^4R^5)_m-$, $-NR-(CR^4R^5)_m-$, $-C(O)O-(CR^4R^5)_m-$, or $-C(O)NR-(CR^4R^5)_m-$. In still other embodiments, L is $-(CR^4R^5)_m-$, $-O-(CR^4R^5)_m-$, $-S(O)_q-(CR^4R^5)_m-$, or $-NR-(CR^4R^5)_m-$. In certain embodiments, L is $-(CR^4R^5)_m-$ or $-O-(CR^4R^5)_m-$, and in others, L is $-O-(CR^4R^5)_m-$. In some such embodiments R⁴ and R⁵ are each hydrogen. In other such embodiments, m = 1-2. In certain embodiments, L and A together are $-(CR^4R^5)_m-COOR$ or $-O-(CR^4R^5)_m-COOR$. In yet other embodiments, R⁴ and R⁵ are, at each occurrence, independently hydrogen, F, Cl, Br, I, substituted or unsubstituted straight or branched C₁₋₄ alkyl, substituted or unsubstituted C₂₋₄ alkenyl, OR, COOR, -NRR; or R⁴ and R⁵, together with the carbon to which they are attached, form a carbonyl.

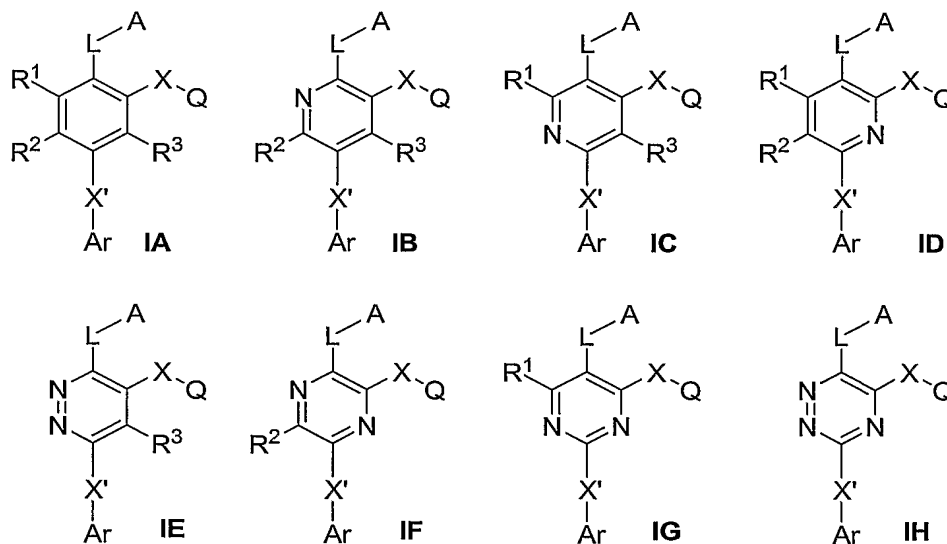
[0014] As indicated above, the length of the linker L in compounds of Formula I may vary depending upon the choice of the integer, m. In some embodiments, m = 1-3 and in others m = 1 or 2. Similarly, the length of the linker X may vary depending upon the choice of the integer, r. In some embodiments, r = 1-3 or r = 1-2. In other embodiments r is 0.

[0015] In some embodiments of compounds having Formula I, X is $-(CR^6R^7)_r-$, $-O-(CR^6R^7)_r-$, $-S(O)_q-(CR^6R^7)_r-$, $-NR-(CR^6R^7)_r-$, $-NR-C(O)-(CR^6R^7)_r-$, $-C(O)O-(CR^6R^7)_r-$, $-C(O)NR-(CR^6R^7)_r-$, $-NR-C(O)-O(CR^6R^7)_r-$, or $-NR-C(O)NR-(CR^6R^7)_r-$. In other embodiments, X is $-(CR^6R^7)_r-$, $-O-(CR^6R^7)_r-$, $-S(O)_q-(CR^6R^7)_r-$, $-NR-(CR^6R^7)_r-$, $-C(O)O-(CR^6R^7)_r-$, or $-C(O)NR-(CR^6R^7)_r-$. In still other embodiments, X is $-(CR^6R^7)_r-$, $-O-(CR^6R^7)_r-$, or $-S(O)_q-(CR^6R^7)_r-$. In yet other embodiments, X is $-(CR^6R^7)_r-$ and preferably, X is $-CH_2-$.

[0016] In some embodiments of compounds having Formula I, Q is a substituted or unsubstituted cycloalkyl or substituted or unsubstituted cycloalkenyl. In other embodiments, Q is a substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl. In yet other embodiments, Q is a substituted or unsubstituted aryl or substituted or unsubstituted aralkyl. In still other embodiments, Q is a fused or unfused bicyclic ring selected from the group consisting of substituted and unsubstituted C_{9-12} aryl, substituted and unsubstituted C_{7-12} cycloalkyl, substituted and unsubstituted C_{9-12} cycloalkenyl, and substituted and unsubstituted C_{7-12} heterocyclyl. In some embodiments, Q may be a fused or unfused bicyclic ring that is substituted or unsubstituted C_{9-12} aryl, and in particular, may be substituted or unsubstituted 1-naphthyl, 2-naphthyl, or 4-biphenyl. In some such embodiments, X is $-CH_2-$.

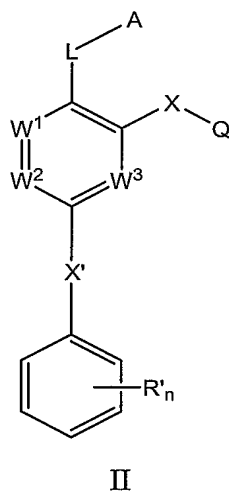
[0017] As indicated above in Formula I, the core ring may be attached to Ar in a variety of ways. In some embodiments, X' is a covalent bond, O, $S(O)_q$, $-NR-$, $-N(C(O)-R)-$, $-N(C(O)-OR)-$, $-N(C(O)-NRR)-$, or substituted or unsubstituted C_{1-4} alkyl. In other embodiments, X' is a covalent bond, O, $S(O)_q$, $-NR-$, $-NR-C(O)-$, $-NR-C(O)-NR-$, substituted or unsubstituted C_{1-2} alkyl, substituted or unsubstituted C_2 alkenyl, or acetylenyl. In other embodiments, X' is a covalent bond, O, $S(O)_q$, or $-NR-$. In still other embodiments, X' is a covalent bond, O, or $-NR-$. Typically, X' is a covalent bond or a substituted or unsubstituted C_{1-2} alkyl such as $-CH_2-$. In some other embodiments, X' may be $-N(C(O)-R)-$, $-N(C(O)-OR)-$, or $-N(C(O)-NRR)-$. In other embodiments, X' is $-N(C(O)-R)-$.

[0018] A variety of 6-member rings are contemplated to be within the scope of compounds having Formula I. In some embodiments, W^1 is CR^1 and in others, W^1 is N. In some embodiments, W^2 is CR^2 and in others, W^2 is N. In certain embodiments, W^3 is CR^3 , and in others, W^3 is N. When W^1 is CR^1 , W^2 is CR^2 , and W^3 is CR^3 , the resulting ring is phenyl substituted by R^1 , R^2 and R^3 . When one of W^1 , W^2 , or W^3 is N and the others are CR^1 and CR^2 , the resulting ring is pyridine substituted by R^1 and R^2 . When W^1 is N, W^2 is N, and W^3 is CR^3 , the resulting ring is pyridazine, substituted by R^3 . When W^1 is CR^1 , W^2 is N, and W^3 is N, the resulting ring is pyrimidine, substituted by R^1 . As will be readily recognized by one of skill in the art, various phenyls, pyridines, pyridazines, pyrazines, pyrimidines, and triazines fall within the scope of the present invention as illustrated by structures IA-IH below, wherein A, L, X, X', Q, Ar, R^1 , R^2 , and R^3 are as defined herein.

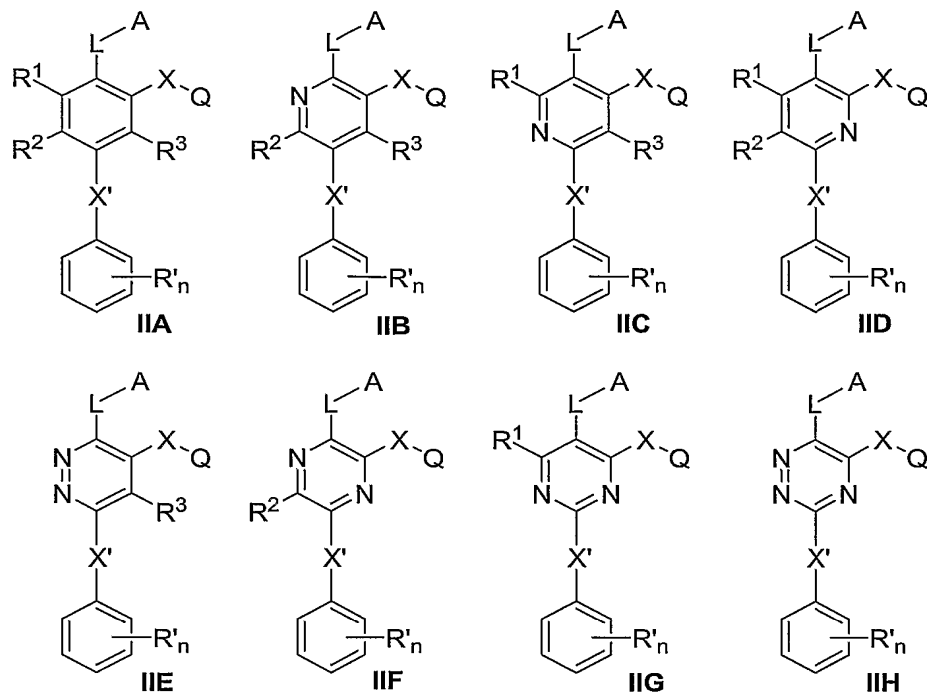


[0019] As reflected by Formula I, numerous rings fall within the definition of Ar. In some embodiments, Ar is a 6-member aryl, a 5- or 6-member heteroaryl, a 9-12 member bicyclic aryl or heterocyclyl, each substituted with one or more R' . In some other embodiments, Ar is a 9-12-member bicyclic aryl or heterocyclyl, substituted with one or more R' . In other embodiments, Ar is a 6-member aryl or a 5- or 6-member heteroaryl, substituted with one or more R' . In yet other embodiments, Ar is a 6-member aryl, substituted with one or more R' . In still other embodiments, Ar is a 5- or 6-member

heteroaryl, substituted with one or more R'. In other embodiments, Ar is substituted with one or more R' and is selected from the group consisting of phenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thiophenyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl and the like. In certain embodiments, Ar is substituted with one or more R' and is selected from the group consisting of phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thiophenyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like. In yet other embodiments, Ar is substituted with one or more R' and is selected from the group consisting of naphthyl, indolyl, benzofuranyl, benzthiazolyl, benzothiophenyl, chromanyl, isochromanyl, coumarinyl, and the like. Commonly, Ar is phenyl substituted with one or more R', to give compounds having Formula II.



[0020] Thus, as those of skill in the art will recognize, when Ar is phenyl, the following structures, IIA-IIIH, are contemplated by this aspect of the present invention, wherein A, L, X, Q, X', R', R¹, R², and R³ are as defined above, and n = 1-5.



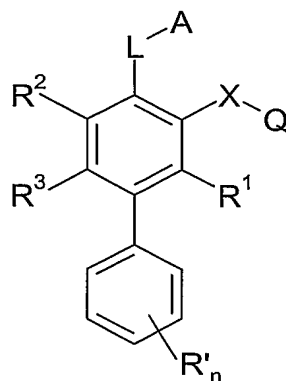
[0021] As described herein, compounds of Formula I may have numerous different substituents. In some embodiments, R^1 , R^2 , and R^3 , at each occurrence, are independently hydrogen, F, Cl, Br, I, CN, NO_2 , substituted or unsubstituted $\text{C}_1\text{-C}_8$ alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted $(\text{C}_{0-6}$ alkylene)(C_{6-14} aryl), substituted or unsubstituted $(\text{C}_{0-6}$ alkylene)(C_{1-13} heterocyclyl), $-\text{OR}^8$, $-\text{C}(\text{O})\text{R}^8$, $-\text{COOR}^8$, $-\text{S}(\text{O})_q\text{R}^8$, $-\text{NR}^8\text{R}^9$, $-\text{C}(\text{O})\text{NR}^8\text{R}^9$, $-\text{N}(\text{R}^8)\text{C}(\text{O})\text{OR}^9$, $-\text{NR}^{10}\text{C}(\text{O})\text{NR}^8\text{R}^9$, $-\text{NR}^{10}\text{C}(\text{NR}^{11})\text{NR}^8\text{R}^9$, $-\text{C}(\text{NR}^{10})\text{NR}^8\text{R}^9$, $-\text{NR}^{10}\text{NR}^8\text{R}^9$, $-\text{NR}^8\text{OR}^9$, $-\text{S}(\text{O})_q\text{NR}^8\text{R}^9$, or $-\text{NR}^8\text{-SO}_2\text{-R}^9$. In other embodiments, R^1 , R^2 , and R^3 , at each occurrence, are independently hydrogen, F, Cl, Br, I, CN, NO_2 , substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted $(\text{C}_{0-6}$ alkylene)(C_{6-14} aryl), substituted or unsubstituted $(\text{C}_{0-6}$ alkylene)(C_{1-13} heterocyclyl), $-\text{OR}^8$, $-\text{C}(\text{O})\text{R}^8$, $-\text{COOR}^8$, $-\text{S}(\text{O})_q\text{R}^8$, $-\text{NR}^8\text{R}^9$, $-\text{C}(\text{Y}')\text{NR}^8\text{R}^9$, $-\text{N}(\text{R}^8)\text{C}(\text{Y}')\text{OR}^9$, $-\text{NR}^{10}\text{C}(\text{NR}^{11})\text{NR}^8\text{R}^9$, $-\text{C}(\text{NR}^{10})\text{NR}^8\text{R}^9$, $-\text{NR}^{10}\text{NR}^8\text{R}^9$, $-\text{NR}^8\text{OR}^9$, $-\text{S}(\text{O})_q\text{NR}^8\text{R}^9$, or $-\text{NR}^8\text{-SO}_2\text{-R}^9$, wherein each Y' is independently O or S.

[0022] As described herein, compounds of Formula I may have numerous different substituents R' on Ar. In some embodiments, R' , at each occurrence, is independently, F,

Cl, Br, I, CN, NO₂, substituted or unsubstituted C₁₋₈ alkyl, substituted or unsubstituted C₂₋₈ alkenyl, substituted or unsubstituted (C₁₋₆ alkylene)(C₆₋₁₄ aryl), substituted or unsubstituted (C₁₋₆ alkylene)(C₁₋₁₃ heterocyclyl), -OR⁸, -C(O)R⁸, -COOR⁸, -S(O)_qR⁸, -NR⁸R⁹, -C(Y)NR⁸R⁹, -N(R⁸)C(Y)OR⁹, -NR¹⁰C(NR¹¹)NR⁸R⁹, -C(NR¹⁰)NR⁸R⁹, -S(O)_qNR⁸R⁹, or -NR⁸-SO₂-R⁹, wherein Y is O or S. In yet other embodiments, R', at each occurrence, is independently F, Cl, Br, I, CN, NO₂, substituted or unsubstituted C₁₋₈ alkyl, substituted or unsubstituted C₂₋₈ alkenyl, substituted or unsubstituted (C₁₋₆ alkylene)(C₆₋₁₄ aryl), substituted or unsubstituted (C₁₋₆ alkylene)(C₁₋₁₃ heterocyclyl), -OR⁸, -C(O)R⁸, -COOR⁸, -NR⁸R⁹, -C(Y)NR⁸R⁹, or -N(R⁸)C(Y)OR⁹, wherein Y is O or S. In other embodiments, R', at each occurrence, is independently F, Cl, Br, I, NO₂, substituted or unsubstituted C₁₋₈ alkyl, substituted or unsubstituted C₂₋₈ alkenyl, OR⁸, or -COOR⁸. In some embodiments, when L and A together are -O-C(O)-CH₃, X' is a covalent bond, and Ar is phenyl substituted by -C(O)-R⁸, R⁸ cannot be phenyl substituted with acetoxy. In yet other embodiments, where L and A together are NH₂, X' is a covalent bond, and Ar is phenyl, Ar is not substituted by NH₂. In some embodiments, where L and A together are -CH(CH₃)₂, Ar is phenyl, and X' is a covalent bond, R² and R' are not both isopropyl. In other embodiments, wherein Ar is phenyl, X' is a covalent bond, X and Q together are benzyl and L and A together are CH₂CH₂COOCl or CH₂CH₂COOH, Ar cannot be substituted by a single alkoxy, and in particular a single methoxy group.

[0023] In certain embodiments of compounds having Formula I, R⁸ and R⁹, together with the nitrogen to which they are attached, form a substituted or unsubstituted heterocyclyl. In some such embodiments, the heterocyclyl is selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and the like.

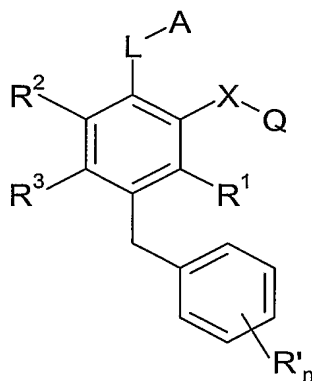
[0024] In some embodiments of compounds having Formula I, W¹ is CR¹, W² is CR², W³ is CR³, X' is a covalent bond, and Ar is phenyl, to give compounds of Formula V:



(V)

wherein A, L, X, Q, R' , R^1 , R^2 , and R^3 are as defined above, and $n = 1-5$. In some embodiments, A is hydrogen, $-COOR$, $-C(O)NROH$, $-C(O)CF_3$, $-B(OH)_2$, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, $-OR$, $-CN$, $-NRR$, $-NO_2$, $-R$, $-COOR$, $-C(O)NRR$, $-OC(O)R$, $-NRC(O)R$, $-OC(O)NR$, and $-NRC(O)OR$. In other embodiments, L is $-(CR^4R^5)_m-$, $-O-(CR^4R^5)_m-$, $-S(O)_q-(CR^4R^5)_m-$, $-NR-(CR^4R^5)_m-$, $-NR-C(O)-(CR^4R^5)_m-$, $-C(O)O-(CR^4R^5)_m-$, $-C(O)NR-(CR^4R^5)_m-$, $-NR-C(O)-O-(CR^4R^5)_m-$, or $-NR-C(O)NR-(CR^4R^5)_m-$. In yet other embodiments, L is $-(CR^4R^5)_m-$ or $-O-(CR^4R^5)_m-$. In some other embodiments, L and A together are $-(CR^4R^5)_m-COOR$ or $-O-(CR^4R^5)_m-COOR$.

[0025] In some embodiments of compounds having Formula I, W^1 is CR^1 , W^2 is CR^2 , W^3 is CR^3 , Ar is phenyl and X' is CH_2 , to give compounds of Formula VI:



(VI)

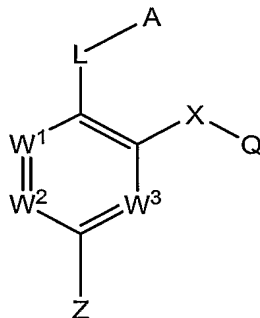
wherein A, L, X, Q, R', R¹, R², and R³ are as defined above, and n = 1-5. In some embodiments, A is hydrogen, -COOR, -C(O)NROH, -C(O)CF₃, -B(OH)₂, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, -OR, -CN, -NRR, -NO₂, -R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR. In other embodiments, L is -(CR⁴R⁵)_m-, -O-(CR⁴R⁵)_m-, -S(O)_q-(CR⁴R⁵)_m-, -NR-(CR⁴R⁵)_m-, -NR-C(O)-(CR⁴R⁵)_m-, -C(O)O-(CR⁴R⁵)_m-, -C(O)NR-(CR⁴R⁵)_m-, -NR-C(O)-O(CR⁴R⁵)_m-, or -NR-C(O)NR-(CR⁴R⁵)_m-. In yet other embodiments, L is -(CR⁴R⁵)_m- or -O-(CR⁴R⁵)_m-. In some embodiments, L and A together are -(CR⁴R⁵)_m-COOR or -O-(CR⁴R⁵)_m-COOR.

[0026] In another aspect, the present invention provides a pharmaceutical composition, comprising a pharmaceutically effective amount of a compound as described herein and a pharmaceutically acceptable carrier or diluent.

[0027] In accordance with yet another aspect of the present invention, there are provided methods for the inhibition of cell entry by viruses and the treatment of viral infections. In particular there are provided methods for the inhibition of cell entry by viruses, the methods comprising contacting a virus with a compound described herein. Viruses that may be inhibited by these methods include HIV, ebola, HRSV, and influenza. The methods of treatment of viral infections include administering a pharmaceutical composition of a compound described herein to a subject in need thereof. Viral infections that may be treated using this method include HIV, ebola, HRSV, and influenza infection. Typically the viral infection is HIV infection (AIDS).

[0028] In still another aspect, the present invention provides methods of preparing a compound having Formula I, wherein X' is a covalent bond or NH, the methods comprising

reacting a compound of Formula III



(III)

with a compound of Formula IV



(IV)

in the presence of a palladium catalyst, a base, and a solvent,

under conditions suitable to form a compound of Formula I, wherein X' is a covalent bond or NH, and wherein

A, Ar, L, X, Q, W¹, W², and W³ are as defined herein;

Z is B(OR'')₂ or NH₂, and Z' is I, Br, Cl, or OTf; or

Z is I, Br, Cl, or OTf, and Z' is B(OR'')₂ or NH₂; and

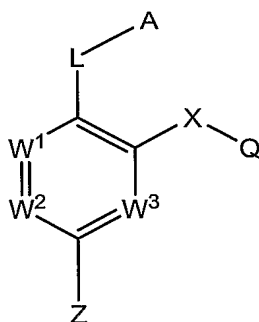
wherein each R'' is independently hydrogen or substituted or unsubstituted alkyl, or, each R'', together with B and the atoms to which they are attached, form a cyclic boronate.

[0029] Conditions to perform the Pd-catalyzed cross coupling reaction between organoboron compounds and organic halides or triflates, known as the Suzuki reaction, are well known in the art [“Recent Advances in the Cross-Coupling Reactions of organoboron Derivatives with Organic Electrophiles”, A. Suzuki *J.Organomet. Chem.* **1999**, 576, 147-

168]. Typically, the palladium catalysts contemplated for use in the practice of the present invention include $\text{Pd}_2(\text{dba})_3$, $\text{Pd}(\text{OAc})_2$, $\text{PdCl}_2(\text{PPh}_3)_2$ and $\text{Pd}(\text{PPh}_3)_4$, among others. Suitable bases contemplated for use in the practice of the present invention include inorganic bases, such as Na_2CO_3 , K_2CO_3 , NaOtBu , and K_3PO_4 , and organic bases, such as TEA, DIEA, DIA and DBU, while suitable solvents include DMF, toluene, or a mixture of DME, ethanol and toluene.

[0030] The invention further provides methods of preparing compounds of Formula I wherein X' is O, the methods comprising

reacting a compound of Formula III



(III)

with a compound of Formula IV



(IV)

in the presence of a copper catalyst, a base, and a solvent,

under conditions suitable to form a compound of Formula I in which X' is O, wherein

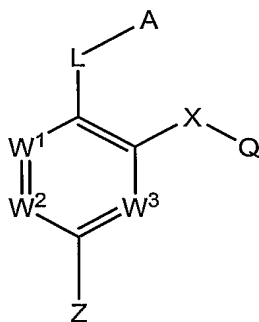
A, Ar, L, X, Q, Z, W^1 , W^2 , and W^3 are as defined herein;

Z is OH, and Z' is I, Br, Cl, or OTf; or Z is I, Br, Cl, or OTf, and Z' is OH.

[0031] Conditions to perform the Cu-catalyzed cross coupling reaction between phenol compounds and organic halides are well known in the art [“Recent Advances in Diaryl Ether Synthesis”, J.S. Sawyer *Tetrahedron* **2000**, 56, 5045-5065]. Typically, the copper catalysts contemplated for use in the practice of the present invention include a Cu(I) catalyst such as CuI, CuBr·SMe₂, Cu(OAc)₂, CuCl, and (CuOTf)₂·PhH. Suitable bases contemplated for use in the practice of the present invention include inorganic bases, such as Cs₂CO₃ and K₂CO₃, and organic bases, such as TEA, and suitable solvents include acetonitrile, toluene, benzene and the like. The reaction is preferably conducted in the presence of a solubilizing entity, e.g., an organic ester such as EtOAc.

[0032] In still another aspect, the present invention provides methods of preparing a compound having Formula I, wherein X' is -CH(OH)-, the methods comprising

reacting a compound of Formula III



(III)

with a compound of Formula IV

Z'-Ar

(IV)

in the presence of a solvent,

under conditions suitable to form a compound of Formula I wherein X' is -CH(OH)-, and wherein

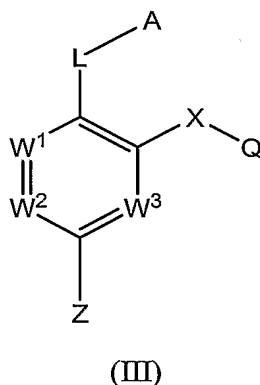
A, Ar, L, X, Q, W¹, W², and W³ are as defined herein;

Z is Li, and Z' is -C(O)-H; or Z is -C(O)-H, and Z' is Li.

[0033] Suitable solvents contemplated for use in the practice of the present invention include ethereal solvents such as THF and diethylether.

[0034] The compound of Formula I wherein X' is -CH₂- can be obtained, for example, by treating the compound of Formula I wherein X' is -CH(OH)- with a reducing agent in a solvent. Reducing agents contemplated for use in the practice of the present invention include H₂ in the presence of Pd/C or triethylsilane with trifluoroacetic acid. Suitable solvents include EtOAc and DCM.

[0035] In still another aspect, the invention provides intermediates for use in the synthesis of compounds of Formula I, the intermediates having the Formula III:



wherein,

A is hydrogen, OH, NO₂, -COOR, -C(O)NROH, -C(O)CF₃, -B(OH)₂, -SO₃H, -PO₃R₂, -OPO₃R₂, -C(O)NHSO₂R, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, -OR, -CN, -NRR, -NO₂, -R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR;

L is $-(\text{CR}^4\text{R}^5)_m-$, $-\text{O}-(\text{CR}^4\text{R}^5)_m-$, $-\text{S}(\text{O})_q-(\text{CR}^4\text{R}^5)_m-$, $-\text{NR}-(\text{CR}^4\text{R}^5)_m-$,
 $-\text{C}(\text{O})\text{O}-(\text{CR}^4\text{R}^5)_m-$, $-\text{C}(\text{O})\text{NR}-(\text{CR}^4\text{R}^5)_m-$, $-\text{NR}-\text{C}(\text{O})-\text{O}(\text{CR}^4\text{R}^5)_m-$,
 $-\text{NR}-\text{C}(\text{O})\text{NR}-(\text{CR}^4\text{R}^5)_m-$, $-\text{S}(\text{O})_2-\text{NR}-(\text{CR}^4\text{R}^5)_m-$, or $-\text{NR}-\text{S}(\text{O})_2-(\text{CR}^4\text{R}^5)_m-$;

W^1 is N or CR^1 ;

W^2 is N or CR^2 ;

W^3 is N or CR^3 ;

X is $-(\text{CR}^6\text{R}^7)_r-$, $-\text{O}-(\text{CR}^6\text{R}^7)_r-$, $-\text{S}(\text{O})_q-(\text{CR}^6\text{R}^7)_r-$, $-\text{NR}-(\text{CR}^6\text{R}^7)_r-$,
 $-\text{C}(\text{O})\text{O}-(\text{CR}^6\text{R}^7)_r-$, $-\text{C}(\text{O})\text{NR}-(\text{CR}^6\text{R}^7)_r-$, $-\text{NR}-\text{C}(\text{O})-\text{O}(\text{CR}^6\text{R}^7)_r-$, $-\text{NR}-\text{C}(\text{O})\text{NR}-(\text{CR}^6\text{R}^7)_r-$,
 $-\text{S}(\text{O})_2-\text{NR}-(\text{CR}^6\text{R}^7)_r-$, or $-\text{NR}-\text{S}(\text{O})_2-(\text{CR}^6\text{R}^7)_r-$;

Q is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

Z is $\text{B}(\text{OR}'')_2$, NH_2 , OH , I , Br , Cl , $\text{C}(\text{O})-\text{H}$, Li or OTf ;

wherein each R'' is independently hydrogen or substituted or unsubstituted alkyl, or, each R'' together with B and the atoms to which they are attached, form a cyclic boronate;

R at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted $(\text{C}_{0-4}$ alkylene)(C_{6-10} aryl), or substituted or unsubstituted $(\text{C}_{0-4}$ alkylene)(C_{1-9} heterocyclyl);

$m = 0 - 4$;

each q is independently 0 - 2; and

$r = 0 - 3$;

and stereoisomers thereof, tautomers thereof, and solvates thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0036] In one aspect, the compounds according to the present invention generally comprise a first planar moiety directly or indirectly attached to an acidic moiety, a hydrophobic planar moiety, and a second planar moiety, as described above. In another aspect, compounds of the present invention are defined by Formulas I and II, as described above. While not wishing to be bound by theory, compounds of the invention are believed to be inhibitors of gp41 folding in viruses such as HIV. Specifically, the compounds are believed to inhibit the formation of a fusion-critical hexameric helical bundle conformation of gp41. Thus, the compounds are believed to interfere with viral entry into cells of the host organism.

[0037] Compounds of the present invention include stereoisomers as well as optical isomers, e.g. mixtures of enantiomers as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in selected compounds of the present series. The present invention also includes isomers and isoforms, defined below, of the compounds of Formula I.

[0038] The term tautomers refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in aqueous solution, ketones are typically in equilibrium with their enol forms. Thus, ketones and their enols are referred to as tautomers of each other. As readily understood by one skilled in the art, a wide variety of functional groups and other structures may exhibit tautomerism, and all tautomers of compounds having Formula I are within the scope of the present invention.

[0039] The compounds of Formula I may also be solvated, especially hydrated. Hydration may occur during manufacturing of the compounds or compositions comprising the compounds, or the hydration may occur over time due to the hygroscopic nature of the compounds.

[0040] Certain compounds within the scope of Formula I are derivatives referred to as prodrugs. The expression "prodrug" denotes a derivative of a direct acting drug, e.g. esters and amides, which derivative has enhanced delivery characteristics and therapeutic value as compared to the drug, and is transformed into the active drug by an enzymatic or chemical process; see Notari, R.E., "Theory and Practice of Prodrug Kinetics," *Methods in Enzymology* 112:309-323 (1985); Bodor, N., "Novel Approaches in Prodrug Design," *Drugs of the Future* 6:165-182 (1981); and Bundgaard, H., "Design of Prodrugs: Bioreversible-Derivatives for Various Functional Groups and Chemical Entities," in *Design of Prodrugs* (H. Bundgaard, ed.), Elsevier, New York (1985), Goodman and Gilmans, *The Pharmacological Basis of Therapeutics*, 8th ed., McGraw-Hill, Int. Ed. 1992. The preceding references and all references listed herein are hereby incorporated in their entirety by reference.

[0041] A "pharmaceutically acceptable salt" includes a salt with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. As salts of inorganic bases, the invention includes, for example, alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. As salts of organic bases, the invention includes, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. As salts of inorganic acids, the instant invention includes, for example, hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. As salts of organic acids, the instant invention includes, for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. As salts of basic amino acids, the instant invention includes, for example, arginine, lysine and ornithine. Acidic amino acids include, for example, aspartic acid and glutamic acid.

[0042] Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium.

[0043] The phrase “unsubstituted alkyl” refers to alkyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}(\text{CH}_2\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{C}(\text{CH}_2\text{CH}_3)_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{C}(\text{CH}_2\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_2\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, and others. The phrase also includes cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and such rings substituted with straight and branched chain alkyl groups as defined above (e.g., cyclopentylmethyl, cyclohexylethyl, and the like). The phrase also includes polycyclic alkyl groups such as, but not limited to, adamantyl, norbornyl, and bicyclo[2.2.2]octyl and such rings substituted with straight and branched chain alkyl groups as defined above. Thus, the phrase unsubstituted alkyl groups includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Unsubstituted alkyl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound. Preferred unsubstituted alkyl groups include straight and branched chain alkyl groups and cyclic alkyl groups having 1 to 20 carbon atoms, and more preferred such groups have from 1 to 10 carbon atoms. Even more preferred such groups, also known as unsubstituted lower alkyl groups, have from 1 to 5 carbon atoms. Most preferred unsubstituted alkyl groups include straight and branched chain alkyl groups having from 1 to 3 carbon atoms and include methyl, ethyl, propyl, and $-\text{CH}(\text{CH}_3)_2$.

[0044] The phrase “substituted alkyl” refers to an unsubstituted alkyl group as defined above in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atoms such as, but not limited to, a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and

aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkyl diarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. Substituted alkyl groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a bond to a heteroatom such as oxygen in groups such as carbonyls, carboxyls, and esters; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. Preferred substituted alkyl groups include, among others, alkyl groups in which one or more bonds to a carbon or hydrogen atom is/are replaced by one or more bonds to fluorine atoms. One example of a substituted alkyl group is the trifluoromethyl group and other alkyl groups that contain the trifluoromethyl group. Other alkyl groups include those in which one or more bonds to a carbon or hydrogen atom is replaced by a bond to an oxygen atom such that the substituted alkyl group contains a hydroxyl, alkoxy, aryloxy group, or heterocycloxy group. Still other alkyl groups include alkyl groups that have an amine, alkylamine, dialkylamine, arylamine, (alkylene)(aryl)amine, diarylamine, heterocyclamine, (alkylene)(heterocycl)amine, (aryl)(heterocycl)amine, or diheterocyclamine group.

[0045] The term “alkylene” refers to saturated, divalent straight or branched chain alkyl groups typically having in the range of about 1 up to about 20 carbon atoms, and “substituted alkylene” refers to alkylene groups further bearing one or more substituents as set forth above for substituted alkyl groups with respect to unsubstituted alkyl groups.

[0046] The phrase “unsubstituted aryl” refers to aryl groups that do not contain heteroatoms. Thus the phrase includes, but is not limited to, groups such as phenyl, biphenyl, anthracenyl, naphthyl by way of example. Although the phrase “unsubstituted aryl” includes groups containing condensed rings such as naphthalene, it does not include aryl groups that have other groups such as alkyl or halo groups bonded to one of the ring members, as aryl groups such as tolyl are considered herein to be substituted aryl groups as described below. A preferred unsubstituted aryl group is phenyl. Unsubstituted aryl

groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound, however.

[0047] The phrase “substituted aryl group” has the same meaning with respect to unsubstituted aryl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. However, a substituted aryl group also includes aryl groups in which one of the aromatic carbons is bonded to one of the non-carbon or non-hydrogen atoms described above and also includes aryl groups in which one or more aromatic carbons of the aryl group is bonded to a substituted and/or unsubstituted alkyl, alkenyl, or alkynyl group as defined herein. This includes bonding arrangements in which two carbon atoms of an aryl group are bonded to two atoms of an alkyl, alkenyl, or alkynyl group to define a fused ring system (e.g. dihydronaphthyl or tetrahydronaphthyl). Thus, the phrase “substituted aryl” includes, but is not limited to tolyl, and hydroxyphenyl among others.

[0048] The phrase “unsubstituted alkenyl” refers to straight and branched chain and cyclic groups such as those described with respect to unsubstituted alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Examples include, but are not limited to vinyl, $-\text{CH}=\text{CH}(\text{CH}_3)$, $-\text{CH}=\text{C}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)=\text{CH}_2$, $-\text{C}(\text{CH}_3)=\text{CH}(\text{CH}_3)$, $-\text{C}(\text{CH}_2\text{CH}_3)=\text{CH}_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others. Preferred unsubstituted alkenyl groups include straight and branched chain alkenyl groups and cycloalkenyl groups having 1 to 20 carbon atoms, and more preferred such groups have from 1 to 10 carbon atoms.

[0049] The phrase “substituted alkenyl” has the same meaning with respect to unsubstituted alkenyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkenyl group includes alkenyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon double bonded to another carbon and those in which one of the non-carbon or non-hydrogen atoms is bonded to a carbon not involved in a double bond to another carbon. Preferred unsubstituted alkenyl groups have from 2 to 20 carbons, and more preferred such groups have from 2 to 10 carbons.

[0050] The phrase “unsubstituted alkynyl” refers to straight and branched chain groups such as those described with respect to unsubstituted alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms. Examples include, but are not limited to $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{C}(\text{CH}_3)$, $-\text{C}\equiv\text{C}(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{C}\equiv\text{C}(\text{CH}_3)$, and $-\text{CH}_2\text{C}\equiv\text{C}(\text{CH}_2\text{CH}_3)$ among others. Preferred unsubstituted alkynyl groups have from 2 to 20 carbons, and more preferred such groups have from 2 to 10 carbons.

[0051] The phrase “substituted alkynyl” has the same meaning with respect to unsubstituted alkynyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkynyl group includes alkynyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon triple bonded to another carbon and those in which a non-carbon or non-hydrogen atom is bonded to a carbon not involved in a triple bond to another carbon.

[0052] The phrase “unsubstituted aralkyl” refers to unsubstituted alkyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkyl group is replaced with a bond to an aryl group as defined above. For example, methyl ($-\text{CH}_3$) is an unsubstituted alkyl group. If a hydrogen atom of the methyl group is replaced by a bond to a phenyl group, such as if the carbon of the methyl were bonded to a carbon of benzene, then the compound is an unsubstituted aralkyl group (*i.e.*, a benzyl group). Thus the phrase includes, but is not limited to, groups such as benzyl, diphenylmethyl, and 1-phenylethyl ($-\text{CH}(\text{C}_6\text{H}_5)(\text{CH}_3)$) among others.

[0053] The phrase “substituted aralkyl” has the same meaning with respect to unsubstituted aralkyl groups that substituted aryl groups had with respect to unsubstituted aryl groups. However, a substituted aralkyl group also includes groups in which a carbon or hydrogen bond of the alkyl part of the group is replaced by a bond to a non-carbon or a non-hydrogen atom. Examples of substituted aralkyl groups include, but are not limited to, $-\text{CH}_2\text{C}(=\text{O})(\text{C}_6\text{H}_5)$, and $-\text{CH}_2(2\text{-methylphenyl})$ among others.

[0054] The phrase “unsubstituted heterocyclyl” refers to both aromatic and nonaromatic ring compounds including monocyclic, bicyclic, and polycyclic ring

compounds containing 3 or more ring members of which one or more is a heteroatom such as, but not limited to, N, O, and S. Although the phrase “unsubstituted heterocyclyl” includes condensed heterocyclic rings such as benzimidazolyl, it does not include heterocyclyl groups that have other groups such as alkyl or halo groups bonded to one of the ring members as compounds such as 2-methylbenzimidazolyl are substituted heterocyclyl groups. Examples of heterocyclyl groups include, but are not limited to: unsaturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridinyl, dihydropyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl etc.), tetrazolyl, (e.g. 1H-tetrazolyl, 2H tetrazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl; condensed unsaturated heterocyclic groups containing 1 to 4 nitrogen atoms such as, but not limited to, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl; unsaturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, morpholinyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzoxazolyl, benzoxadiazolyl, benzoxazinyl (e.g. 2H-1,4-benzoxazinyl etc.); unsaturated 3 to 8 membered rings containing 1 to 3 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolodinyl; saturated and unsaturated 3 to 8 membered rings containing 1 to 2 sulfur atoms such as, but not limited to, thienyl, dihydrodithiinyl, dihydrodithionyl, tetrahydrothiophene, tetrahydrothiopyran; unsaturated condensed heterocyclic rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, benzothiazolyl, benzothiadiazolyl, benzothiazinyl (e.g. 2H-1,4-benzothiazinyl, etc.), dihydrobenzothiazinyl (e.g. 2H-3,4-dihydrobenzothiazinyl, etc.), unsaturated 3 to 8 membered rings containing oxygen atoms such as, but not limited to furyl; unsaturated condensed heterocyclic rings containing 1 to 2 oxygen atoms such as, but not limited to,

benzodioxolyl (e.g. 1,3-benzodioxoyl, etc.), chromanyl, isochromanyl, coumindinyl; unsaturated 3 to 8 membered rings containing an oxygen atom and 1 to 2 sulfur atoms such as, but not limited to, dihydrooxathiinyl; saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 2 sulfur atoms such as 1,4-oxathiane; unsaturated condensed rings containing 1 to 2 sulfur atoms such as benzothieryl, benzodithieryl; and unsaturated condensed heterocyclic rings containing an oxygen atom and 1 to 2 oxygen atoms such as benzoxathiinyl. Heterocyclyl group also include those described above in which one or more S atoms in the ring is double-bonded to one or two oxygen atoms (sulfoxides and sulfones). For example, heterocyclyl groups include tetrahydrothiophene oxide and tetrahydrothiophene 1,1-dioxide. Preferred heterocyclyl groups contain 5 or 6 ring members. More preferred heterocyclyl groups include morpholine, piperazine, piperidine, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiophene, thiomorpholine, thiomorpholine in which the S atom of the thiomorpholine is bonded to one or more O atoms, pyrrole, homopiperazine, oxazolidin-2-one, pyrrolidin-2-one, oxazole, quinuclidine, thiazole, isoxazole, furan, and tetrahydrofuran.

[0055] The phrase “substituted heterocyclyl” refers to an unsubstituted heterocyclyl group as defined above in which one or more of the ring members is bonded to a non-hydrogen atom such as described above with respect to substituted alkyl groups and substituted aryl groups. Examples include, but are not limited to, 2-methylbenzimidazolyl, 5-methylbenzimidazolyl, 5-chlorobenzthiazolyl, 1-methyl piperazinyl, 2-phenoxy-thiophene, and 2-chloropyridinyl among others. In addition, substituted heterocyclyl groups also include heterocyclyl groups in which the bond to the non-hydrogen atom is a bond to a carbon atom that is part of a substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, or unsubstituted heterocyclyl group. Examples include but are not limited to 1-benzylpiperidinyl, 3-phenylthiomorpholinyl, 3-(pyrrolidin-1-yl)-pyrrolidinyl, and 4-(piperidin-1-yl)-piperidinyl.

[0056] The phrase “unsubstituted heterocyclylalkyl” refers to unsubstituted alkyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkyl group is replaced with a bond to a heterocyclyl group as defined above. For example,

methyl (-CH₃) is an unsubstituted alkyl group. If a hydrogen atom of the methyl group is replaced by a bond to a heterocyclyl group, such as if the carbon of the methyl were bonded to carbon 2 of pyridine (one of the carbons bonded to the N of the pyridine) or carbons 3 or 4 of the pyridine, then the compound is an unsubstituted heterocyclylalkyl group.

[0057] The phrase “substituted heterocyclylalkyl” has the same meaning with respect to unsubstituted heterocyclylalkyl groups that substituted aralkyl groups had with respect to unsubstituted aralkyl groups. However, a substituted heterocyclylalkyl group also includes groups in which a non-hydrogen atom is bonded to a heteroatom in the heterocyclyl group of the heterocyclylalkyl group such as, but not limited to, a nitrogen atom in the piperidine ring of a piperidinylalkyl group. In addition, a substituted heterocyclylalkyl group also includes groups in which a carbon bond or a hydrogen bond of the alkyl part of the group is replaced by a bond to a substituted and unsubstituted aryl or substituted and unsubstituted aralkyl group. Examples include but are not limited to phenyl-(piperidin-1-yl)-methyl and phenyl-(morpholin-4-yl)-methyl.

[0058] The phrase “unsubstituted heteroaryl” refers to unsubstituted heterocyclyl groups which are aromatic. The phrase “substituted heteroaryl” has the same meaning with respect to unsubstituted heteroaryl groups as substituted heterocyclyl groups have with respect to unsubstituted heterocyclyl groups. Examples of substituted and unsubstituted heteroaryl groups are given above under substituted and unsubstituted heterocyclyl groups.

[0059] The phrase “unsubstituted alkoxy” refers to a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of an otherwise unsubstituted alkyl group as defined above.

[0060] The phrase “substituted alkoxy” refers to a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of an otherwise substituted alkyl group as defined above.

[0061] As employed herein, the term “biaryl” refers to any molecule having two or more aryl groups.

[0062] For medicinal use, the pharmaceutically acceptable acid addition salts, i.e., those salts in which the anion does not contribute significantly to toxicity or pharmacological activity of the organic cation, are preferred. The acid addition salts are obtained either by reaction of an organic base of Formula I with an organic or inorganic acid, preferably by contact in solution, or by any of the standard methods detailed in the literature available to any practitioner skilled in the art. Examples of useful organic acids are carboxylic acids such as maleic acid, acetic acid, lactic acid, trifluoroacetic acid, tartaric acid, propionic acid, fumaric acid, isethionic acid, succinic acid, cyclamic acid, pivalic acid and the like; useful inorganic acids are hydrohalide acids such as HCl, HBr, HI; sulfuric acid; phosphoric acid and the like. Preferred acids for forming acid addition salts include HCl, trifluoroacetic acid, and acetic acid.

[0063] The compounds of the present invention are useful for diagnosing and treating HIV infection. Methods of administering and doses for the compounds of the present invention are addressed below. The compounds of the present invention in isotopically labelled form are useful as a diagnostic agent. The isotopically labelled form of the compound is administered to a patient and detection devices are used to create an image based on the presence of the compound in particular parts of the body. Typically, radiation imaging cameras employ a conversion medium (wherein the high energy gamma ray is absorbed, displacing an electron which emits a photon upon its return to the orbital state), photoelectric detectors arranged in a spatial detection chamber (to determine the position of the emitted photons), and circuitry to analyze the photons detected in the chamber and produce an image.

[0064] Also within the scope of the invention is the use of any of the compounds according to Formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

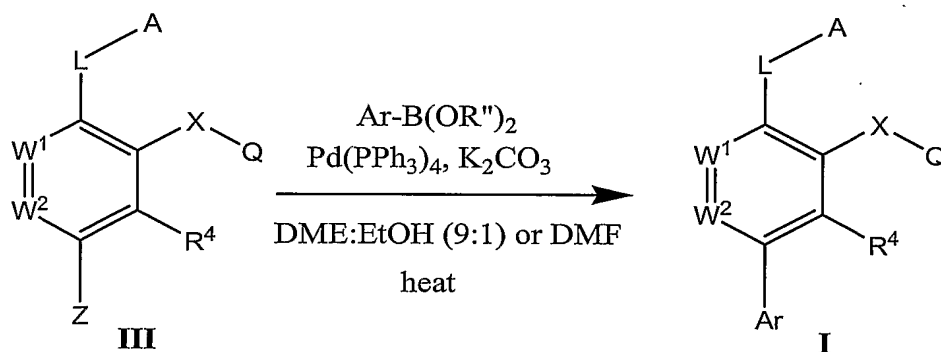
[0065] A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to Formula I above, is administered to a patient in need of such treatment. Further discussion of methods for treating patients, including doses and methods of administration is discussed below, in relation to pharmaceutical compositions.

[0066] Any compound of Formula I can be used to treat and/or diagnose any of the conditions listed above. The foregoing examples are for illustration and are not meant to limit the invention in any way. It is to be understood from these examples that the compounds of Formula (1) can be used to treat any of the foregoing conditions.

Methods of Preparation

[0067] In one aspect, the invention provides methods for preparing the compounds of the invention, as described above. For example, the invention provides methods for the preparation of compounds of Formula I, wherein X' is a covalent bond, by Pd catalyzed cross-coupling (Suzuki Coupling) as the key step to form the biaryl structures. Schemes 1 and 2 illustrate typical coupling procedures wherein L, A, X, Q, R², R³, R⁴, W¹, W², and W³ are as defined in Formula I. In Scheme 1, Z is a leaving group such as Cl, Br, I, or triflate (OTf) and each R'' is independently hydrogen or substituted or unsubstituted alkyl, or, taken together, a cyclic boronate.

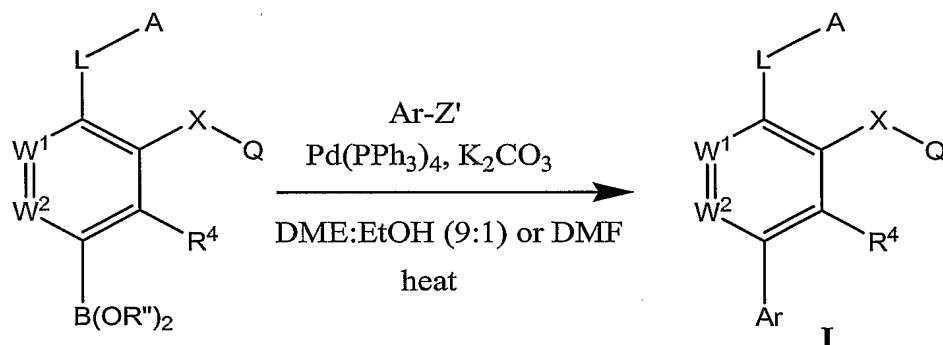
Scheme 1



[0068] In Scheme 2, Z' is a leaving group such as Cl, Br, I, or OTf, and R'' is as defined in Scheme 1. Those of skill in the art will readily understand that other palladium

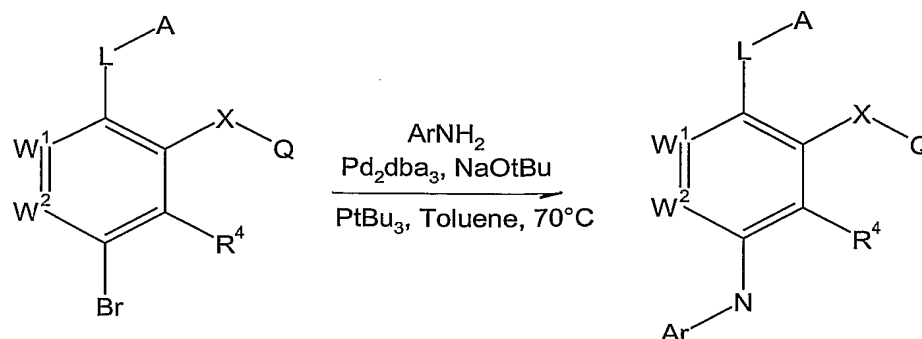
catalysts in addition to $\text{Pd}(\text{PPh}_3)_4$ may be used in the coupling reaction such as $\text{Pd}(\text{OAc})_2$, $\text{PdCl}_2(\text{PPh}_3)_2$, and $\text{Pd}_2(\text{dba})_3$. Similarly, in addition to K_2CO_3 , other bases such as Na_2CO_3 , Cs_2CO_3 or Et_3N may be employed in the coupling reaction. Suitable solvents for the reaction include DMF, DME/toluene/EtOH (9:1:1), toluene, DME, benzene, benzene/EtOH (9:1) as well as DME/EtOH (9:1).

Scheme 2



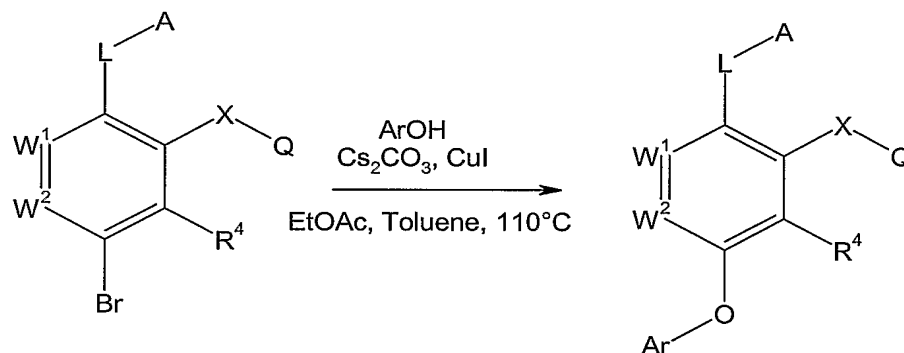
[0069] In addition, the invention provides methods for the preparation of compounds of Formula I, wherein X' is, e.g., N or O. Scheme 3 illustrates the palladium catalyzed addition of amines to aryl and heteroaryl rings having a halide such as bromine to give compounds of the invention. The reaction is carried out in the presence of a palladium catalyst such as $\text{Pd}_2(\text{dba})_3$ or others as described above, a base such as NaOtBu , and a phosphine such as tri-*t*-butylphosphine. Typically the reaction is performed in toluene, but benzene or other solvents may also be used. The reaction may be heated to about 60-110 °C; typically 70 °C is sufficient, but higher or lower temperatures may also be used. The X' nitrogen may be subsequently acylated, by reaction with an activated carbonyl such as an anhydride or an acid chloride in the presence of a base such as TEA. Typically the reaction is performed in dichloromethane, but other solvents may also be used. The reaction may be heated, but typically is performed at room temperature.

Scheme 3



[0070] Scheme 4 shows the copper catalyzed addition of phenols or other hydroxyl containing rings to aryl and heteroaryl rings having a halide such as bromine. The reaction is carried out in the presence of about 5 mole percent EtOAc, a base such as Cs_2CO_3 and a Cu(I) catalyst such as CuI. Those of skill in the art will understand that any suitable solvent may be used; toluene works well. Typically, the reaction is heated to about 80-140 °C, preferably to 110 °C, but higher or lower temperatures may be used.

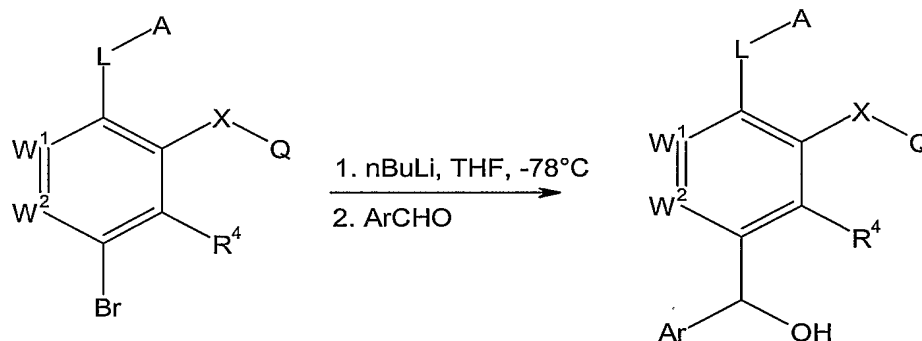
Scheme 4



[0071] In addition, the invention provides methods for the preparation of compounds of Formula I, wherein X' is $-\text{CH}(\text{OH})-$. Scheme 5 illustrates the metal halogen exchange of aryl and heteroaryl rings having a halide such as bromine, followed by addition of aryl or heteroaryl aldehydes to the lithiated intermediate to give compounds of the invention. Typically the metal halogen exchange reaction is performed by reaction of the halide containing compound with $n\text{BuLi}$ in THF, but diethylether or other solvents may also be used. The lithiated species is subsequently reacted *in situ* with aryl or

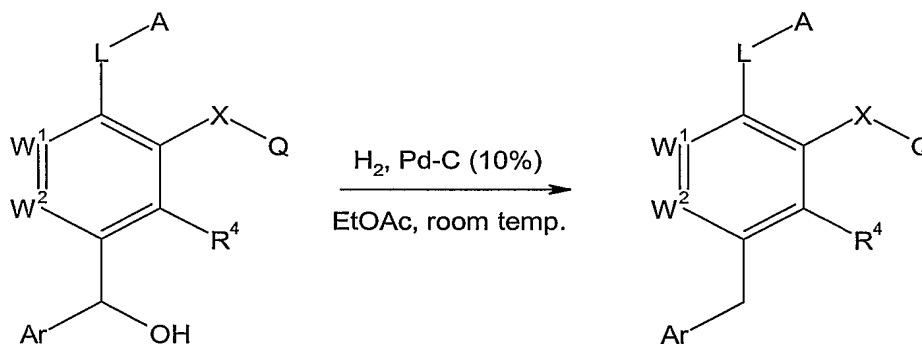
heteroaryl aldehydes. The one-pot reaction is typically performed at -78°C , but higher or lower temperatures may also be used.

Scheme 5



[0072] The invention also provides methods to obtain compounds of Formula I wherein X' is $-\text{CH}_2-$. Scheme 6 illustrates the reduction of compounds of Formula I wherein X' is $-\text{CH}(\text{OH})-$ with a reducing agent to obtain compounds of the present invention wherein X' is $-\text{CH}_2-$. Typically the reducing agent is H_2 in the presence of Pd/C or triethylsilane with trifluoroacetic acid. Typically the solvent is EtOAc or DCM , but other solvents may be used.

Scheme 6



[0073] Additional techniques to make the compounds of the present invention, such as catalyzed and uncatalyzed ring closure and ring addition reactions, are well known to those of skill in the art.

Pharmaceutical Compositions

[0074] The compounds of the present invention may be formulated as pharmaceutical compositions comprising the molecules of the present invention.

[0075] The pharmaceutical compositions of the invention can be administered to any animal that can experience the beneficial effects of the compounds of the invention. Preferably, the animal is a mammal, and foremost among such mammals are humans, although the invention is not intended to be so limited. The term "subject" as used herein therefore means any animal that can experience the beneficial effects of the compounds of the invention.

[0076] The pharmaceutical compositions of the present invention can be administered by any means that achieve their intended purpose. For example, administration can be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, topical, intranasal, intrathoracic, epidural, intrathecal, intracerebroventricular or ocular routes, or by injection into the joints. Alternatively, or concurrently, administration can be by the oral route. Preferred routes of administration are oral, intravenous or intramuscular.

[0077] In addition to the pharmacologically active compounds, the new pharmaceutical preparations can contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically.

[0078] The pharmaceutical preparations of the present invention are manufactured in a manner that is, itself, known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[0079] Suitable excipients are, in particular, fillers such as carbohydrates or saccharides, for example, lactose, sucrose, dextrans, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as, starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone, and antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or excipients or other stabilizers and/or buffers. If desired, disintegrating agents can be added, such as, the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as, sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as, magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings that, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol, and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as, acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses. Detergents can also be used to stabilize or to increase or decrease the absorption of the pharmaceutical composition, including liposomal carriers.

[0080] Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives which are particularly useful for preventing the growth or action of microorganisms. Various preservatives are well known and include, e.g., phenol and ascorbic acid. One skilled in the art would appreciate that the choice of a pharmaceutically acceptable carrier including a physiologically acceptable compound depends, for example, on the route of administration of the compound of the invention and on its particular physio-chemical characteristics.

[0081] Examples of aqueous solutions that can be used in formulations for enteral, parenteral or transmucosal drug delivery include, e.g., water, saline, phosphate buffered saline, Hank's solution, Ringer's solution, dextrose/saline, glucose solutions and the like. The formulations can contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as buffering agents, tonicity adjusting agents, wetting agents, detergents and the like. Additives can also include additional active ingredients such as bactericidal agents, or stabilizers. For example, the solution can contain sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate or triethanolamine oleate. These compositions can be sterilized by conventional, well-known sterilization techniques, or can be sterile filtered. The resulting aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. The concentration of compound in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs.

[0082] Solid formulations can be used for enteral (oral) administration. They can be formulated as, e.g., pills, tablets, powders or capsules. For solid compositions, conventional nontoxic solid carriers can be used which include, e.g., pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. For oral administration, a pharmaceutically acceptable nontoxic composition is formed by incorporating any of the normally employed excipients, such as those carriers previously listed, and generally 10% to 95% of active ingredient (e.g., compound or compounds of the present invention). A non-solid formulation can also be used for enteral administration. The carrier can be selected from various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like. Suitable pharmaceutical excipients include e.g., starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol.

[0083] Compositions of the invention, when administered orally, can be protected from digestion. This can be accomplished either by complexing with additional components in a composition to render it resistant to acidic and enzymatic hydrolysis or by packaging the compound(s) of the present invention in an appropriately resistant carrier such as a liposome. Means of protecting compounds from digestion are well known in the art, see, e.g., Fix (1996) Pharm Res. 13:1760-1764; Samanen (1996) J. Pharm. Pharmacol. 48:119-135; U.S. Patent 5,391,377, describing lipid compositions for oral delivery of therapeutic agents (liposomal delivery is discussed in further detail, *infra*).

[0084] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated can be used in the formulation. Such penetrants are generally known in the art, and include, e.g., for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents can be used to facilitate permeation. Transmucosal administration can be through nasal sprays or using suppositories. For topical, transdermal administration, the agents are formulated into ointments, creams, salves, powders and gels. Transdermal delivery systems can also include, e.g., patches.

[0085] Compositions of the invention can also be administered in sustained delivery or sustained release mechanisms, which can deliver the formulation internally. For example, biodegradable microspheres or capsules or other biodegradable polymer configurations capable of sustained delivery of a compound can be included in the formulations of the invention (see, e.g., Putney (1998) Nat. Biotechnol. 16:153-157).

[0086] For inhalation, the compounds of the invention can be delivered using any system known in the art, including dry powder aerosols, liquids delivery systems, air jet nebulizers, propellant systems, and the like. For example, the pharmaceutical formulation can be administered in the form of an aerosol or mist. For aerosol administration, the formulation can be supplied in finely divided form along with a surfactant and propellant. In another aspect, the device for delivering the formulation to respiratory tissue is an inhaler in which the formulation vaporizes. Other liquid delivery systems include, e.g., air jet nebulizers.

[0087] In preparing pharmaceuticals of the present invention, a variety of formulation modifications can be used and manipulated to alter pharmacokinetics and biodistribution. A number of methods for altering pharmacokinetics and biodistribution are known to one of ordinary skill in the art. Examples of such methods include protection of the compositions of the invention in vesicles composed of substances such as proteins, lipids (for example, liposomes, see below), carbohydrates, or synthetic polymers (discussed above). For a general discussion of pharmacokinetics, see, e.g., Remington's, Chapters 37-39.

[0088] Compositions of the invention can be delivered alone or as pharmaceutical compositions by any means known in the art, e.g., systemically, regionally, or locally (e.g., directly into, or directed to, a tumor); by intraarterial, intrathecal (IT), intravenous (IV), parenteral, intra-pleural cavity, topical, oral, or local administration, as subcutaneous, intra-tracheal (e.g., by aerosol) or transmucosal (e.g., buccal, bladder, vaginal, uterine, rectal, nasal mucosa). Actual methods for preparing administrable compositions will be known or apparent to those skilled in the art and are disclosed in detail in the scientific and patent literature, see e.g., Remington's. For a "regional effect," e.g., to focus on a specific organ, one mode of administration includes intra-arterial or intrathecal (IT) injections, e.g., to focus on a specific organ, e.g., brain and CNS (see e.g., Gurun (1997) Anesth Analg. 85:317-323). For example, intra-carotid artery injection is preferred where it is desired to deliver the compound(s) of the invention directly to the brain. Parenteral administration is a preferred route of delivery if a high systemic dosage is needed. Actual methods for preparing parenterally administrable compositions will be known or apparent to those skilled in the art and are disclosed in detail, in e.g., Remington's. See also, Bai (1997) J. Neuroimmunol. 80:65-75; Warren (1997) J. Neurol. Sci. 152:31-38; Tonegawa (1997) J. Exp. Med. 186:507-515.

[0089] In one aspect, the pharmaceutical formulations comprising the compounds of the invention are incorporated in lipid monolayers or bilayers, e.g., liposomes, see, e.g., U.S. Patent No. 6,110,490; 6,096,716; 5,283,185; 5,279,833. The invention also provides formulations in which water soluble compounds of the invention have been attached to the surface of the monolayer or bilayer. For example, the compounds of the invention can be

attached to hydrazide- PEG- (distearoylphosphatidyl) ethanolamine- containing liposomes (see, e.g., Zalipsky (1995) *Bioconjug. Chem.* 6:705-708). Liposomes or any form of lipid membrane, such as planar lipid membranes or the cell membrane of an intact cell, e.g., a red blood cell, can be used. Liposomal formulations can be by any means, including administration intravenously, transdermally (see, e.g., Vutla (1996) *J. Pharm. Sci.* 85:5-8), transmucosally, or orally. The invention also provides pharmaceutical preparations in which the compounds of the invention are incorporated within micelles and/or liposomes (see, e.g., Suntres (1994) *J. Pharm. Pharmacol.* 46:23-28; Woodle (1992) *Pharm. Res.* 9:260-265). Liposomes and liposomal formulations can be prepared according to standard methods and are also well known in the art, see, e.g., Remington's; Akimaru (1995) *Cytokines Mol. Ther.* 1:197-210; Alving (1995) *Immunol. Rev.* 145:5-31; Szoka (1980) *Ann. Rev. Biophys. Bioeng.* 9:467; U.S. Pat. Nos. 4, 235,871, 4,501,728 and 4,837,028.

[0090] The pharmaceutical compositions of the invention can be administered in a variety of unit dosage forms depending upon the method of administration. Dosages for pharmaceutical compositions are well known to those of skill in the art. Such dosages are typically advisory in nature and are adjusted depending on the particular therapeutic context, patient tolerance, etc. The amount of compound adequate to accomplish this is defined as a "therapeutically effective dose." The dosage schedule and amounts effective for this use, i.e., the "dosing regimen," will depend upon a variety of factors, including the stage of the disease or condition, the severity of the disease or condition, the general state of the patient's health, the patient's physical status, age, pharmaceutical formulation and concentration of active agent, and the like. In calculating the dosage regimen for a patient, the mode of administration also is taken into consideration. The dosage regimen must also take into consideration the pharmacokinetics, i.e., the pharmaceutical composition's rate of absorption, bioavailability, metabolism, clearance, and the like. Any factors which are normally considered when determining the individual regimen and dosage level as the most appropriate for a particular patient can be considered when determining dosages. Preferred unit dosages are from about 1 gram to about 1 mg, about 700 mg to about 5 mg, about 650 mg to about 10 mg, about 600 mg to about 20 mg, about 550 mg to about 25 mg, about 500 mg to about 30 mg, about 450 mg to about 40 mg, about 400 mg to about

50 mg, about 350 mg to about 100 mg, about 300 mg to about 150 mg, about 350 mg to about 200 mg. Even more preferably, the dosages are from about 150 mg to about 5 mg, from about 100 mg to about 5 mg, from about 50 mg to about 5 mg, from about 25 mg to about 5 mg, from about 20 mg to about 5 mg, from about 15 to about 5 mg, from about 10 to about 5 mg, from about 10 mg to about 1 mg, from about 10 mg to about 2 mg, from about 10 mg to about 4 mg, and from about 5 to about 0.5 mg.

[0091] Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as, glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as, fatty oils or liquid paraffin. In addition, stabilizers may be added.

[0092] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts, alkaline solutions and cyclodextrin inclusion complexes. Especially preferred salts are hydrochloride and acetate salts. One or more modified or unmodified cyclodextrins can be employed to stabilize and increase the water solubility of compounds of the present invention. Useful cyclodextrins for this purpose are disclosed in U.S. Pat. Nos. 4,727,064, 4,764,604, and 5,024,998.

[0093] In addition, suspensions of the active compounds as appropriate oily injection suspensions can be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

[0094] Compounds of Formula I can be labelled with radioactive iodine as described below or by using an exchange reaction. Exchange of hot iodine for cold iodine is well known in the art. Alternatively, a radioiodine labelled compound can be prepared from the corresponding bromo compound via a tributylstannyl intermediate. See, U.S. Pat. No. 5,122,361, herein incorporated by reference.

[0095] The present invention also includes compositions comprising a compound of Formula I complexed with a radioactive atom.

[0096] The present invention also includes diagnostic compositions, comprising a pharmaceutically acceptable carrier and a diagnostically effective amount of compositions derived from the compounds of Formula I.

[0097] The "diagnostically effective amount" of the composition required as a dose will depend on the route of administration, the type of mammal being treated, and the physical characteristics of the specific mammal under consideration. These factors and their relationship to determining this dose are well known to skilled practitioners in the medical diagnostic arts. Also, the diagnostically effective amount and method of administration can be tailored to achieve optimal efficacy but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize. In any regard, the dose for imaging should be sufficient for detecting the presence of the imaging agent at the site of a thrombus in question. Typically, radiologic imaging will require that the dose provided by the pharmaceutical composition of the present invention be about 5 to 20 μCi , preferably about 10 μCi . Magnetic resonance imaging will require that the dose provided be about 0.001 to 5 mmole/kg, preferably about 0.005 to 0.5 mmole/kg of a compound of Formula I complexed with paramagnetic atom. In either case, it is known in the art that the actual dose will depend on the specific application.

[0098] "Pharmaceutically acceptable carriers" for in vivo use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The pharmaceutical

compositions of the present invention may be formulated with a pharmaceutically acceptable carrier to provide sterile solutions or suspensions for injectable administration. In particular, injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspensions in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, mannitol, lactose, lecithin, albumin, sodium glutamate, cysteine hydrochloride, or the like. In addition, if desired, the injectable pharmaceutical compositions may contain minor amounts of nontoxic auxiliary substances, such as wetting agents, pH buffering agents, and the like. If desired, absorption enhancing preparations (e.g., liposomes) may be utilized.

[0099] The present invention also encompasses diagnostic compositions prepared for storage or administration. These would additionally contain preservatives, stabilizers and dyes. For example, sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid may be added as preservatives. In addition, antioxidants and suspending agents may be used.

[00100] The radioactive atoms associated with the compositions and diagnostic compositions of the present invention are preferably imaged using a radiation detection means capable of detecting gamma radiation, such as a gamma camera or the like.

[00101] The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

Screening Methodologies

[00102] The compounds of the present invention can be screened against potential targets using high throughput assays and secondary screening procedures, which are both described more fully below. Following screening, a primary candidate is then used as a starting point for optimizing the drug activity by altering its chemical structure. Once a final structure has been selected, the compound will go into pre-clinical and clinical testing.

[00103] The first step in the screening procedure is high throughput screening. High throughput screening typically incorporates integrated robotic systems so that large numbers of test compounds can be tested for antagonist or agonist activity within a short amount of time. These methods include, but are not limited to, homogeneous assay formats such as fluorescence resonance energy transfer, fluorescence polarization, time-resolved fluorescence resonance energy transfer, scintillation proximity assays, reporter gene assays, protein fragment complementation assays, fluorescence quenched enzyme substrate, chromogenic enzyme substrate and electrochemiluminescence, as well as more traditional heterogeneous assay formats such as enzyme-linked immunosorbant assays (ELISA) or radioimmunoassays. The molecules of the present invention can be screened by procedures known in the art. Preferably, the following screening assays are used: NC-1 ELISA, HIV-1 Mediated Cell-to-Cell Fusion, and Detection of HIV-1-Mediated Cytopathic Effect (CPE) and in Vitro Cytotoxicity (Debnath *et al.*, "Structure-Based Identification of Small Molecule Antiviral Compounds Targeted to the gp41 Core Structure of the Human Immunodeficiency Virus Type I," *J. Med. Chem.* 42:3203-3209 (1999)). A preferred screening assay is NC-1 ELISA. *Id.*

[00104] Homogeneous assays are mix-and-read style assays that are very amenable to robotic application, whereas heterogeneous assays require separation of free from bound analyte by more complex unit operations such as filtration, centrifugation or washing. These assays are utilized to detect a wide variety of specific biomolecular interactions and the inhibition thereof by small organic molecules, including protein-protein, receptor-ligand, enzyme-substrate interactions, and so on. These assay methods and techniques are well known in the art (see, e.g., *High Throughput Screening: The Discovery of Bioactive Substances*, John P. Devlin (ed.), Marcel Dekker, New York, 1997 ISBN: 0-8247-0067-8).

[00105] The compounds of the present invention can be screened using advanced high throughput screening techniques, such as sequential high throughput screening (SHTS) which is the iterative process of screening a sample of compounds for activity, analyzing the results, and selecting a new set of compounds for screening, based on what has been learned from the previous screens. Selection of compounds is driven by finding

structure activity relationships (SARs) within the screened compounds and using those relationships to drive further selection.

[00106] Recursive partitioning (RP) is an advanced statistical methodology that can be used in conjunction with advanced high throughput screening techniques, such as SHTS, by identifying relationships between specific chemical structural features of the molecules and biological activity. The premise is that the biological activity of a compound is a consequence of its molecular structure. Accordingly, it is very useful to identify those aspects of molecular structure that are relevant to a particular biological activity. By gaining a better understanding of the mechanism by which the compound acts, additional compounds for screening can more accurately be selected.

[00107] Quantitative structure activity relationship (QSAR) models are determined using sets of compounds whose molecular structure and biological activity are known, a training set. QSAR approaches are either linear or nonlinear. The linear approach assumes that the activity varies linearly with the level of whatever features affect it, and that there are no interactions among the different features.

[00108] Nonlinear QSAR approaches account for the fact that activity can result from threshold effects; a feature must be present at least some threshold level for activity to occur. Furthermore, interactions between features are observed in many QSAR settings, the utility of one feature depending upon the presence of another. Activity may require the simultaneous presence of two features. In particular, a molecule may be active if some optimal distance separates two features. If the features are too close, the compound is inactive. If the features are too far apart, then the compound is inactive.

[00109] Recursive partitioning (RP) methods (Hawkins, D.M. and Kass, G.V., (1982) Automatic Interaction Detection. In *Topics in Applied Multivariate Analysis*; Hawkins, D. H., Ed.; Cambridge University Press, pp. 269-302; Breiman, L., Friedman, J. Olshen, R. and Stone, C. (1984) *Classification and Regression Trees*. Chapman and Hall) can be used in nonlinear QSAR analysis. RP methods are able to model nonlinear relationships, even in the presence of strong interaction between the predictors. The output

of a recursive partitioning analysis is a dendrogram (tree) in which predictors are used to progressively split the data set into smaller and more homogeneous subsets. If some node in the dendrogram contains mainly active compounds, then the detailed path by which its molecules are split out provides a clue to the molecular structures that are associated with activity. The path to a node whose cases are predominantly inactive is a clue to the molecular structures that have no bearing on or that actively inhibit activity. Hawkins, D.M., Young, S.S., and Rusinko, A. III (1997) "Analysis of a large structure-activity data set using recursive partitioning," *Quant. Struct.-Act. Relat.* 16:296-302 (1997) provide an illustration of the analysis of a screening data set using FIRM.

[00110] There are two standard uses for the dendrogram. First, its structure provides an indication of which predictors are important for explaining the dependent variable. The other use is as a method of prediction; by following a future case with unknown dependent variable down to the final terminal node into which it falls based upon its independent variables, one may use the mean of the data in that node as a predictor of the new observation. Rusinko, A. III, Farmen, M.W., Lambert, C.G., Brown, P.L., and Young, S.S. (1999) "Analysis of a large structure/biological activity data set using recursive partitioning," *J. Chem. Inf. Comput. Science* 39:1017-1026 demonstrate the predictive power of RP to achieve a 1500% hit rate increase over random for MAO inhibitors.

[00111] Following primary screening procedures, which identify a set of molecules for further study, secondary screening procedures can be used. Secondary screening operations differ from primary screening assays mostly in their requirements for lower throughput and the need to handle more complicated functional assay protocols. Secondary screening can be as simple as a confirmatory assay subsequent to a high throughput screen or as complicated as a cellular assay involving complicated cell functions or the measurement of intracellular phenomena. Appropriate screening assays will be well known to those of skill in the art.

[00112] Preferred secondary screening assays are assays based on interactions between the compounds of the present invention and living cells, cellular structures or biomolecules. Preferred are cell-based assays which provide information about how a

compound is likely to interact in a biological system, not just about how it interacts with a potential drug target. Accordingly, cell-based screening assays provide information regarding potential interactions that may occur within the cell, such interactions that may potentially impact efficacy and/or safety of the compounds being evaluated.

[00113] Information from cellular assays can include cell morphology and/or temporal or spatial information about the cell (and components of the cell)-captured by automated cell analysis systems. These systems typically use image analysis technologies to capture the data and sophisticated informatics software to analyze the results. Alternatively, cell-based assays can use luciferase reporter-gene assays to monitor the impact of a compound. Still another approach involves electrophysiological methods that measure changes in ion concentrations (often focusing on calcium ions) in a cell. An assay can also detect changes in the potential of the cell membrane. Alternatively, assays can be performed that determine the proliferative rate of a target cell population or the rate of apoptosis.

[00114] Cell-based assays can provide information relating to compound properties such as absorption, permeability, selectivity, specificity, and metabolism. As a result, more information is known about the lead compounds that are selected after cell-based screening. The advantages of using intact, living cells for compound screening include: efficacy of compounds can be best predicted by measuring biological behaviour and function in intact cells; molecular interactions can be evaluated within the context of the "working environment" inside the cell; toxicity and nonspecific effects can be identified; drug effects on selective cell types can be distinguished; drug penetration can be evaluated in whole cell studies; orphan targets require cell based functional assays; whole cell assays obviate protein purification & expression steps.

[00115] Examples of secondary cell-based assays include viral titer assays, second messenger assays like luciferase, and fluorescent signal assays. A preferred secondary assay is one based on receptor interaction and signal transduction. Secondary screening techniques are designed to capture complex cellular activities like morphology changes, differentiation, locomotion, apoptosis, adhesion, translocations of signaling molecules,

protein trafficking. (Asa D., "Automating Cell Permeability Assays," *Screening* 1:36 - 37 (2001); Giacomello, E. *et al.*, "Centrifugal Assay for Fluorescence-based Cell Adhesion adapted to the analysis of *ex vivo* cells and capable of determining relative binding strength," *BioTechniques* 26:758 – 766 (1999); Neumayer, J. and R. Perris, "Cytotoxicity Studies Using Microplate Fluorometry for Quantification," *BioForum International* 2(4):173 - 176 (1998); Parker G.J. *et al.*, "Development of High Throughput Screening Assays using Fluorescence Polarization: nuclear receptor-ligand binding and kinase/phosphatase assays," *Journal of Biomolecular Screening* 5(2):77 – 88 (2000)).

[00116] Another major application of cell-based assays is in toxicity screening. A crucial part of drug discovery and development is the screening of drug candidates to eliminate compounds that will cause side effects. Cell-based assays can offer less-expensive, higher-throughput ways to eliminate many of the compounds that may fail these more expensive assays.

[00117] From the secondary assays, one or more lead compounds is (are) discovered. The lead compound often must be optimized to improve potency (typically from 1-5 μM to 1-10 nM) against a specific molecular target, selectivity (100-fold versus related targets) and absence of cytotoxicity, and that physical and chemical properties are appropriate for good oral bioavailability. Correlative and predictive tools to can be used to optimize lead compounds toward development. These include software models that describe molecular characteristics of poorly absorbed or toxic compounds, and experimental assays, including Caco-2 permeability models and liver microsome metabolism models, to facilitate the optimization process.

[00118] Following lead optimization, an animal model is developed which in essence determines not only the compound's affect on the body, but the body's affect on the compound. For example, in animal testing, the amount of compound absorbed into the blood, how the compound is broken down chemically in the body and the toxicity of its breakdown products (i.e. metabolites) is measured. Animals can also give information regarding how quickly the compound and its metabolites are excreted from the body. A metabolite of the compound can be more effective than the compound originally picked for

development. Accordingly, metabolites of the compounds of the present invention are encompassed in the present invention. Preferably, two or more species of animal are typically tested because a compound may affect one species differently from another.

[00119] Following animal testing and FDA approval, testing in humans is conducted. Phase 1 clinical trials mainly determines the safety of the drug, while Phase 2 clinical trials mainly determine the effectiveness of the drug, along with short-term safety. Phase 3 trials test safety, effectiveness and dosage. Guidelines for animal testing and human testing are known to one of skill in the art, and can be found on the Food and Drug Administration's (FDA) web page.

[00120] The following examples are for illustration and are not intended to limit the scope of the present invention in any manner.

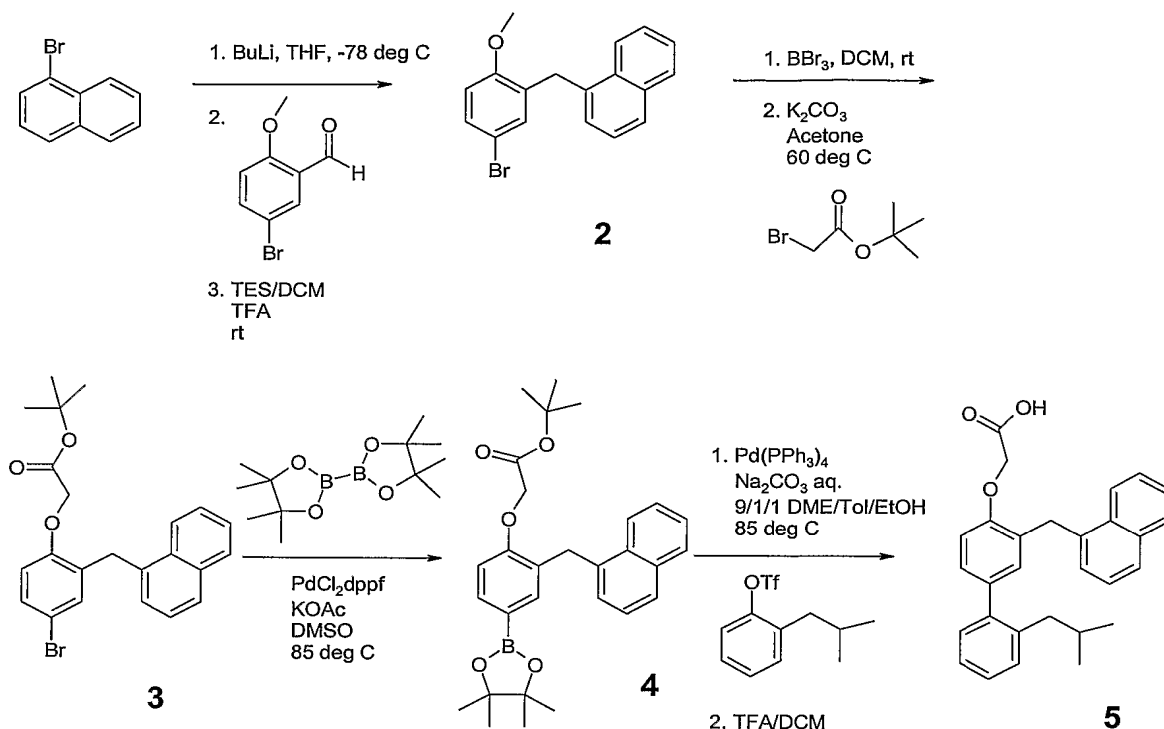
EXAMPLES

[00121] The following abbreviations are used throughout the application with respect to chemical terminology:

aq	Aqueous
Bn	Benzyl
tBu	<i>tert</i> -Butyl
BuLi	Butyl lithium
DBU	1,5-Diazabicyclo[4.3.0]non-5-ene
DCM	Dichloromethane
Deg	Degrees
DIA	Diisopropylamine
DIEA	Diisopropylethylamine
DME	Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
Dppf	Ph ₂ PC ₅ H ₄ FeC ₅ H ₄ PPh ₂

Eqv.	Equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
HPLC	High Pressure Liquid Chromatography
IC ₅₀ value	The concentration of an inhibitor that causes a 50 % reduction in a measured activity.
LAH	Lithium aluminum hydride
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
OTf	Triflate, i.e. -OSO ₂ CF ₃
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
Ph	Phenyl
rt	Room temperature
TEA	Triethylamine
TES	Triethylsilane
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Tol	Toluene

EXAMPLE 1



[00122] **1-(5-Bromo-2-methoxy-benzyl)-naphthalene, 2.** To a solution of 1-bromonaphthalene 1 (1.70 mL, 12.22 mmol) in 40 mL of THF at -78°C was added *n*-BuLi (7.64 mL of a 1.6 M solution in hexanes, 12.22 mmol, 1.00 eqv) via syringe. After stirring for 1 h, a solution of 4-bromo-anisaldehyde (2.63 g, 12.23 mmol, 1.00 eqv) in 30 mL of THF was added dropwise via a dropping funnel. The resulting mixture was stirred for 60 min at -78°C , then for 2 h at -30°C and finally 15 h at rt. The reaction was quenched with 1 M aq HCl and added to Et_2O (100 mL). The organic phase was separated, washed with H_2O , dried over MgSO_4 and concentrated in vacuo. Column chromatography (CH_2Cl_2) yielded 3.70 g of a pale greenish foam (88%): ^1H NMR (500 MHz, CDCl_3) δ 3.84 (s, 3H), 6.80 (d, $J = 8.51$ Hz, 1H), 6.81 (s, 1H), 7.18 (d, $J = 2.68$ Hz, 1H), 7.34 (dd, $J_1 = 8.82$ Hz, $J_2 = 2.52$ Hz, 1H), 7.48 (m, 3H), 7.55 (d, $J = 7.09$ Hz, 1H), 7.79 (d, $J = 8.20$ Hz, 1H), 7.87 (m, 1H), 8.00 (m, 1H); HRMS (EI) Calcd for $\text{C}_{18}\text{H}_{15}\text{BrO}_2$: 342.0255. Found 342.0251.

[00123] To a solution of the compound obtained in the previous reaction (0.57 g, 1.6 mmol) in 30 mL of 1:1 DCM/triethylsilane (TES) was added 1 mL of TFA. The resulting solution was allowed to stand at rt for 5 h. The mixture was concentrated in

vacuo to yield 0.52 g of a white foam (91%): ^1H NMR (400 MHz, CDCl_3) δ 3.87 (s, 3H), 4.37 (s, 2H), 6.79 (d, $J = 8.0$ Hz 1H), 6.94 (s, 1H), 7.26 (m, 2H), 7.46 (m, 3H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 1H).

[00124] (4-Bromo-2-naphthalen-1-ylmethyl-phenoxy)-acetic acid tert-butyl ester, 3. To a solution of **2** (0.52 g, 1.6 mmol) in 100 mL of DCM was added 4.8 mL of a 1 M solution of BBr_3 (3 eqv., 4.8 mmol) in DCM. The solution was allowed to stand at rt for 5 h. The mixture was quenched with H_2O and extracted with DCM. The organic fractions were combined, dried (MgSO_4), filtered, and concentrated in vacuo to yield a crude oil. Column chromatography (30% EtOAc in Hexanes) yielded 0.42 g of a clear oil (84%): ^1H NMR (400 MHz, CDCl_3) δ 4.42 (s, 2H), 4.90 (s, 1H), 6.74 (d, $J = 8.0$ Hz 1H), 7.12 (s, 1H), 7.26 (m, 2H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.52 (m, 2H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 1H).

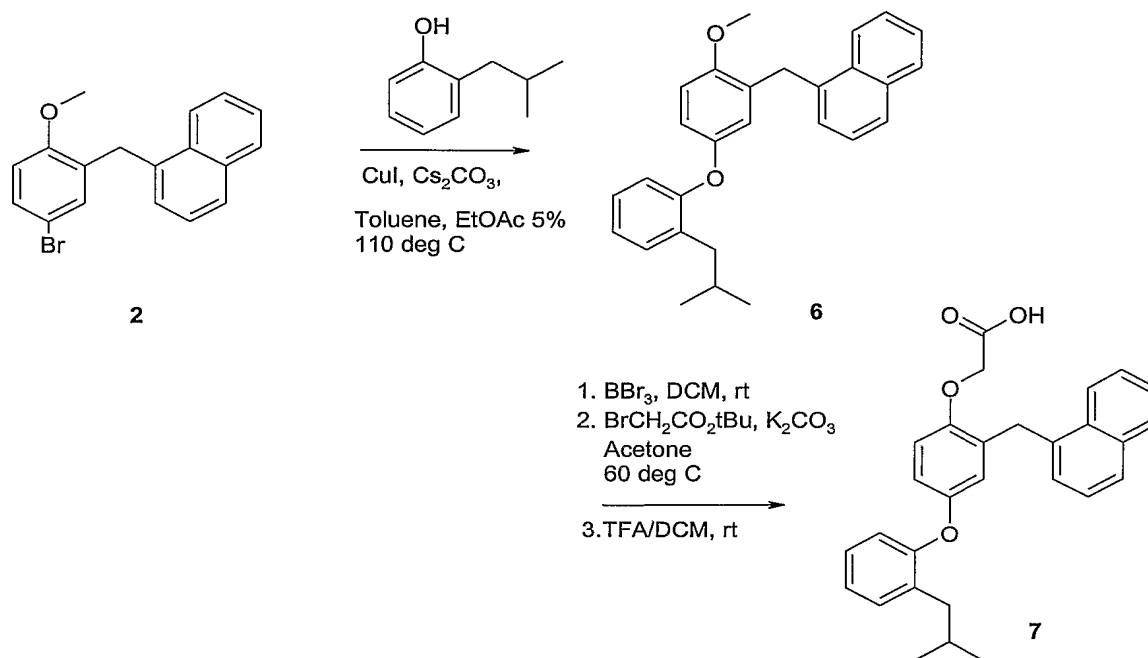
[00125] To a mixture of the compound obtained in the previous reaction (6.78 g, 21.7 mmol) and K_2CO_3 (3 eqv., 9.0 g, 0.065 mol) in 100 mL of acetone was added tert-butyl-bromoacetate (1.05 eqv., 3.4 mL, 22.8 mmol). The solution was refluxed for 12 h. The solution was allowed to cool to rt, added to H_2O , and extracted with DCM. The organic fractions were combined, dried (MgSO_4), filtered, and concentrated in vacuo to yield a crude oil. Column chromatography (30% EtOAc in Hexanes) yielded 8.9 g of a clear oil (96%): ^1H NMR (400 MHz, CDCl_3) δ 1.51 (s, 9H), 4.48 (s, 2H), 4.60 (s, 2H), 6.67 (d, $J = 8.0$ Hz, 1H), 6.97 (s, 1H), 7.30 (m, 2H), 7.48 (m, 3H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H).

[00126] [2-Naphthalen-1-ylmethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-acetic acid tert-butyl ester, 4. In a 40 mL vial were placed **3** (1.0 g, 2.34 mmol), potassium acetate (970 mg, 7.02 mmol), bis(pinacolato)diboron (654 mg, 2.57 mmol), DMSO (14 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (86 mg, 0.12 mmol). The vial was flushed with nitrogen and capped tightly. The suspension was stirred for 3h at 85°C after which time the reaction was partitioned between H_2O and DCM. The aqueous layer was extracted twice with DCM. The organic fractions were combined, dried (MgSO_4), filtered, and concentrated in vacuo to yield a crude oil. Column chromatography (30% EtOAc in Hexanes) yielded 0.83 g of a clear oil

(75%): ^1H NMR (400 MHz, CDCl_3) δ 1.28 (s, 9H), 1.43 (s, 6H), 1.47 (s, 6H), 4.49 (s, 2H), 4.54 (s, 2H), 6.76 (d, $J = 8.33$ Hz, 1H), 7.16 (d, $J = 7.1$ Hz, 1H), 7.35 (d, $J = 7.1$ Hz, 1H), 7.45 (d, $J = 6.8$ Hz, 1H), 7.48 (d, $J = 6.8$ Hz, 1H), 7.58 (d, $J = 1.2$ Hz, 1H), 7.67 (d, $J = 8.3$ Hz, 1H), 7.70 (d, $J = 8.3$ Hz, 1H), 7.84 (d, $J = 7.3$ Hz, 1H), 8.18 (d, $J = 7.8$ Hz, 1H).

[00127] **(2'-Isobutyl-3-naphthalen-1-ylmethyl-biphenyl-4-yloxy)-acetic acid, 5.**
2-Isobutylphenyl trifluoromethanesulfonate (0.100 g, 0.35 mmol), **4** (1.0 eqv., 0.17 g, 0.35 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (10 mol%, 40 mg) were dissolved in 3 mL of 9/1/1 DME/EtOH/Toluene. Na_2CO_3 (0.35 mL of 2 M aq solution, 0.7 mmol, 2 eqv.) was added via syringe and the solution was stirred at 85 °C for 17 h. The reaction mixture was concentrated in vacuo and taken up in 2:1 $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$. The layers were separated and the H_2O layer was extracted further with CH_2Cl_2 . The combined organic fractions were dried (MgSO_4), filtered, and concentrated in vacuo. Column chromatography (30% EtOAc in Hexanes) yielded 0.073 g of a clear oil. The material was dissolved in 2 mL of 1:1:0.05 TFA/DCM/ H_2O and allowed to stand at rt for 12 h. The solution was concentrated in vacuo to yield 0.051 g of a white solid (34%). ^1H NMR (400 MHz, CDCl_3) δ 0.57 (d, $J = 8.0$ Hz, 6H), 1.48 (m, 1H), 2.25 (d, $J = 8.0$ Hz, 2H), 4.57 (s, 2H), 4.82 (s, 2H), 6.88 (s, 1H), 6.90 (s, 1H), 7.14 (m, 5H), 7.31 (d, $J = 8.0$ Hz, 1H), 7.41 (t, $J = 8.0$ Hz, 1H), 7.46 (m, 2H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 8.06 (d, $J = 8.0$ Hz, 1H).

EXAMPLE 2



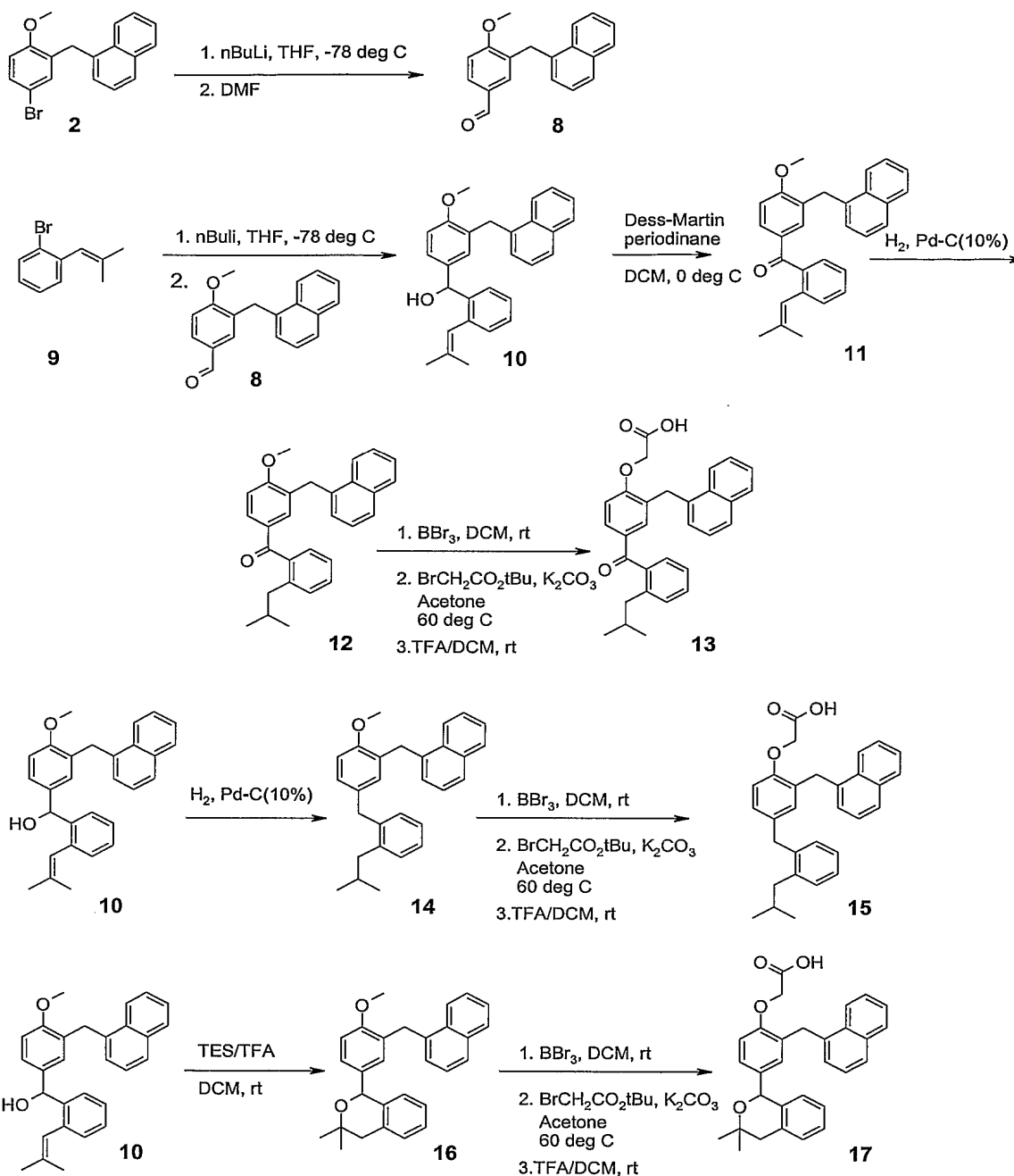
[00128] **4-(2-Isobutyl-phenoxy)-1-methoxy-2-[5-methylene-6-prop-2-en-(Z)-ylidene-cyclohexa-1,3-dienylmethyl]-benzene, 6.** The aryl halide **2** (40 mg, 0.12 mmol), 2-isobutylphenol (25 mg, 0.17 mmol), Cs_2CO_3 (58 mg, 0.018 mmol), CuI (1.1 mg, 0.006 mmol, 5.0 mol % Cu), ethyl acetate (0.5 mg, 0.006 mmol, 5.0 mol %) and toluene (1.0 mL) were added to a 7 mL vial which was then sealed purged with nitrogen and heated at 110°C for 24 hours. The reaction mixture was then allowed to cool down to room temperature, diluted with Et_2O and washed sequentially with 5% aqueous NaOH, H_2O and brine. The organic layer was dried over MgSO_4 and concentrated under vacuum to give the crude product. Purification by flash chromatography (20% EtOAc in hexanes) on silica gel afforded 40 mg (85 %) of the analytically pure compound. ^1H NMR (400 MHz, CDCl_3) δ 0.84 (d, $J = 6.5$ Hz, 6H), 1.89 (m, 1H), 2.45 (d, $J = 7.3$ Hz, 2H), 3.89 (s, 3H), 4.43 (s, 2H), 6.60 (d, $J = 2.8$ Hz, 1H), 6.67 (d, $J = 8.0$ Hz, 1H), 6.76 (dd, $J = 8.0, 3.0$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.95 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.03 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.41 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.47-7.50 (m, 2H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.86-7.92 (m, 1H), 8.00-8.03 (m, 1H).

[00129] [4-(2-Isobutyl-phenoxy)-2-naphthalen-1-ylmethyl-phenoxy]-acetic acid,
7. To a solution of compound 6 (30 mg, 0.07 mmol) in 5 mL of DCM was added 0.21 mL of a 1 M solution of BBr₃ (3 eqv., 0.21 mmol) in DCM. The solution was allowed to stand at rt for 1 h. The mixture was quenched with H₂O and extracted with DCM. The organic fractions were combined, dried (MgSO₄), filtered, and concentrated in vacuum to yield a crude oil. Column chromatography (30% EtOAc in hexanes) yielded 23 mg of a clear oil (95%). ¹H NMR (400 MHz, CDCl₃) δ 0.88 (d, *J* = 6.6 Hz, 6H), 1.93 (m, 1H), 2.49 (d, *J* = 7.1 Hz, 2H), 4.43 (s, 2H), 6.72 (m, 3H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.98 (dd, *J* = 7.3, 7.6 Hz, 1H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.42 (dd, *J* = 7.1, 8.3 Hz, 1H), 7.72 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.89 (m, 2H), 8.07 (m, 2H).

[00130] To a mixture of the compound obtained in the previous reaction (30 mg, 0.06 mmol) and K₂CO₃ (3 eqv., 25 mg, 0.18 mmol) in 1 mL of acetone was added *tert*-butyl-bromoacetate (1.5 eqv., 13 μL, 0.09 mmol). The solution was refluxed for 12 h. The solution was allowed to cool to rt, added to H₂O, and extracted with DCM. The organic fractions were combined, dried (MgSO₄), filtered, and concentrated in vacuum to yield a crude oil. Column chromatography (20% EtOAc in hexanes) yielded 23 mg of a clear oil (96%). ¹H NMR (400 MHz, CDCl₃) δ 0.81 (d, *J* = 6.5 Hz, 6H), 1.51 (s, 9H), 1.85 (m, 1H), 2.41 (d, *J* = 7.3 Hz, 2H), 4.50 (s, 2H), 4.57 (s, 2H), 6.58 (d, *J* = 2.5 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.70 (dd, *J* = 9.3, 2.5 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 8.0, 7.8 Hz, 1H), 7.00 (dd, *J* = 8.0, 8.1 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 8.3, 7.8 Hz, 1H), 7.47 (m, 2H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.88 (m, 1H), 8.04 (m, 1H).

[00131] The *tert*-Butyl ester obtained in the previous step (20 mg, 0.40 mmol) was dissolved in 0.5 mL of 1:1 TFA/DCM and allowed to stand at room temperature for 1 h. The solution was concentrated in vacuum to yield 18 mg of a white solid (95%). ¹H NMR (400 MHz, CDCl₃) δ 0.83 (d, *J* = 6.5 Hz, 6H), 1.87 (m, 1H), 2.43 (d, *J* = 7.3 Hz, 2H), 4.49 (s, 2H), 4.69 (s, 2H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.70 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.74 (dd, *J* = 8.0, 3.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.98 (dd, *J* = 8.0, 7.8 Hz, 1H), 7.00 (dd, *J* = 8.0, 8.1 Hz, 1H), 7.13 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.25 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.40 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.49 (m, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.88 (m, 1H), 8.02 (m, 1H).

EXAMPLE 3



[00132] **4-Methoxy-3-naphthalen-1-ylmethyl-benzaldehyde, 8.** To a solution of **2** (0.5 g, 1.5 mmol) in 5 mL of THF at -78°C was added $n\text{-BuLi}$ (0.75 mL of a 2.0 M solution in hexanes, 1.5 mmol, 1.0 eqv.) via syringe. After stirring for 30 minutes, DMF

(0.58 mL, 7.5 mmol) was added. The resulting mixture was stirred for 30 min at -78 °C. The reaction was quenched with 1 M aq HCl and added to Et₂O (20 mL). The organic phase was separated, washed with H₂O, dried over MgSO₄ and concentrated in vacuum. Column chromatography (EtOAc) yielded 0.4 g of a colorless foam (95%). ¹H NMR (400 MHz, CDCl₃) δ 3.98 (s, 3H), 4.44 (s, 2H), 7.04 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.43 (m, 4H), 7.78 (m, 2H), 7.87 (m, 1H), 7.94 (m, 1H), 8.32 (m, 1H).

[00133] (4-Methoxy-3-naphthalen-1-ylmethyl-phenyl)-[2-(2-methyl-propenyl)-phenyl]-methanol, 10. To a solution of **9** (0.15, 0.72 mmol) in 5 mL of THF at -78 °C was added *n*-BuLi (0.36 mL of a 2.0 M solution in hexanes, 0.72 mmol, 1.00 eqv.) via syringe. After stirring for 1 h, a solution of **8** (0.20 g, 0.72 mmol, 1.00 eqv.) in 1 mL of THF was added dropwise via syringe. The resulting mixture was stirred for 30 min at -78 °C. The reaction was quenched with 1 M aq HCl and added to Et₂O (10 mL). The organic phase was separated, washed with H₂O, dried over MgSO₄ and concentrated in vacuum. Column chromatography (15% of EtOAc in hexanes) yielded 0.26 g of a colorless oil.

[00134] (4-Methoxy-3-naphthalen-1-ylmethyl-phenyl)-[2-(2-methyl-propenyl)-phenyl]-methanone, 11. To a solution of **10** (30 mg, 0.07 mmol) in DCM (1 mL), Dess-Martin periodinane (46 mg, 0.11 mmol, 1.5 eqv.) was added while cooling at 0°C. After 30 min, reaction was completed, the mixture was quenched with H₂O and extracted with DCM. The organic fractions were combined, dried (MgSO₄), filtered, and concentrated in vacuum to yield a crude oil. Column chromatography (10% EtOAc in Hexanes) yielded 21 mg of a clear oil (72%). ¹H NMR (400 MHz, CDCl₃) δ 1.53 (3H, s), 1.60 (3H, s), 3.94 (s, 3H), 4.41 (s, 2H), 5.96 (s, 1H), 6.93 (d, *J* = 8.6 Hz 1H), 7.18 (m, 4H), 7.35 (m, 3H), 7.48 (m, 2H), 7.68 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.87 (m, 1H), 7.99 (m, 1H).

[00135] (2-Isobutyl-phenyl)-(4-methoxy-3-naphthalen-1-ylmethyl-phenyl)-methanone, 12. A mixture of **10** (20 mg, 0.045 mmol) and palladium on charcoal (10%) (0.10 mol%, 0.0045 mmol) in EtOAc (0.5 mL) were stirred under hydrogen atmosphere for 30 minutes. Then the reaction was filtered through celite and evaporated in vacuum to give 17 mg of a crude oil that was used in the next step without purification.

[00136] **[4-(2-Isobutyl-benzoyl)-2-naphthalen-1-ylmethyl-phenoxy]-acetic acid, 13.** To a solution of **12** (17 mg, 0.04 mmol) in 1 mL of DCM was added 0.16 mL of a 1 M solution of BBr₃ (3 eqv., 0.16 mmol) in DCM. The solution was allowed to stand at rt for 1 h. The mixture was quenched with H₂O and extracted with DCM. The organic fractions were combined, dried (MgSO₄), filtered, and concentrated in vacuum to yield a crude oil that was used in the next step without purification

[00137] To a mixture of the compound obtained in the previous step (15 mg, 0.04 mmol) and K₂CO₃ (3 eqv., 15 mg, 0.12 mmol) in 1 mL of acetone was added *tert*-butyl-bromoacetate (1.05 eqv., 6 μ l, 0.042 mmol). The solution was refluxed for 12 h. The solution was allowed to cool to rt, added to H₂O, and extracted with DCM. The organic fractions were combined, dried (MgSO₄), filtered, and concentrated in vacuum to yield a crude oil.

[00138] The *tert*-Butyl ester (obtained in the previous reaction) was dissolved in 1 mL of 1:1 TFA/DCM and allowed to stand at room temperature for 12 h. The solution was concentrated in vacuum and the residue purified by HPLC to yield 10 mg of a white solid (95%). ¹H NMR (400 MHz, CDCl₃) δ 0.86 (d, *J* = 6.5 Hz, 6H), 1.80 (m, 1H), 2.42 (d, *J* = 6.5 Hz, 1H), 3.95 (s, 1H), 4.40 (2H, s), 6.98 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 7.25 (m, 3H), 7.35 (m, 2H), 7.44 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.53 (d, *J* = 8.0, 7.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 8.27 (d, *J* = 7.6 Hz, 1H).

[00139] **1-[5-(2-Isobutyl-benzyl)-2-methoxy-benzyl]-naphthalene, 14.** A mixture of **10** (90 mg, 0.22 mmol) and palladium on charcoal (10%) (0.10 mol %, 0.022 mmol) in EtOAc (0.5 mL) were stirred under hydrogen atmosphere for 1 hour and 30 minutes. Then the reaction was filtered through celite and evaporated in vacuum to give 80 mg of a crude oil. Column chromatography (10% EtOAc in Hexanes) yielded 40 mg of a clear oil (46%). ¹H NMR (400 MHz, CDCl₃) δ 0.81 (d, *J* = 6.8 Hz, 6H), 1.75 (s, 3H), 2.33 (d, *J* = 7.3 Hz, 3H), 3.81 (s, 2H), 3.86 (s, 3H), 4.40 (s, 2H), 6.70 (s, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 6.8 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 7.21 (m, 3H), 7.40 (dd, *J* = 7.3, 7.8 Hz, 1H), 7.47 (m, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 9.0 Hz, 1H).

[00140] **[4-(2-Isobutyl-benzyl)-2-naphthalen-1-ylmethyl-phenoxy]-acetic acid, 15.** To a solution of **14** (30 mg, 0.07 mmol) in 1 mL of DCM was added 0.21 mL of a 1 M solution of BBr₃ (3 eqv., 0.21 mmol) in DCM. The solution was allowed to stand at rt for 1 h. The mixture was quenched with H₂O and extracted with DCM. The organic fractions were combined, dried (MgSO₄), filtered, and concentrated in vacuum to yield a crude oil that was used without further purification.

[00141] To a mixture of the compound obtained in the previous step (26 mg, 0.07 mmol) and K₂CO₃ (3 eqv., 29 mg, 0.21 mol) in 1 mL of acetone was added *tert*-butyl-bromoacetate (1.05 eq., 31 μ l, 0.21 mmol). The solution was refluxed for 12 h and then allowed to cool to room temperature, added to H₂O, and extracted with DCM. The organic fractions were combined, dried (MgSO₄), filtered, and concentrated in vacuum to yield a crude oil. Column chromatography (20% EtOAc in hexanes) yielded 32 mg of a clear oil (96%). ¹H NMR (400 MHz, CDCl₃) δ 0.79 (d, *J* = 6.6 Hz, 6H), 1.49 (s, 9H), 1.71 (s, 1H), 2.32 (d, *J* = 7.3 Hz, 2H), 3.79 (s, 2H), 4.49 (s, 2H), 7.08 (m, 4H), 7.27 (d, *J* = 7.1 Hz, 1H), 7.45 (m, 3H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H).

[00142] The *tert*-Butyl ester obtained above was dissolved in 1 mL of 1:1 TFA/DCM and allowed to stand at room temperature for 12 h. The solution was concentrated in vacuum to yield 51 mg of a white solid (95%). ¹H NMR (400 MHz, CDCl₃) δ 0.80 (d, *J* = 6.5 Hz, 6H), 1.72 (s, 1H), 2.32 (d, *J* = 7.3 Hz, 2H), 3.80 (s, 2H), 4.42 (s, H), 4.66 (s, 2H), 6.72 (m, 2H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.95 (m, 4H), 7.38 (t, *J* = 8.3 Hz, 1H), 7.45 (m, 3H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H).

[00143] **1-(4-Methoxy-3-naphthalen-1-ylmethyl-phenyl)-3,3-dimethyl-isochroman, 16.** To a solution of **10** (10 mg, 0.02 mmol) in 0.5 mL of 1:1 DCM/triethylsilane (TES) was added 0.05 mL of TFA. The resulting solution was allowed to stand at rt for 5 minutes. The mixture was concentrated in vacuum to yield a crude oil. Column chromatography (20% EtOAc in hexanes) yielded 7 mg of a clear oil (87%). ¹H NMR (400 MHz, CDCl₃) δ 0.54 (s, 3H), 1.08 (s, 3H), 2.68 (c, *J* = 4.5 Hz, 6H), 3.85 (s, 1H), 3.87 (s, 2H), 4.43 (c, *J* = 7.0 Hz, 6H), 6.68 (d, *J* = 2.2 Hz, 1H), 6.90 (m, 3H), 7.05

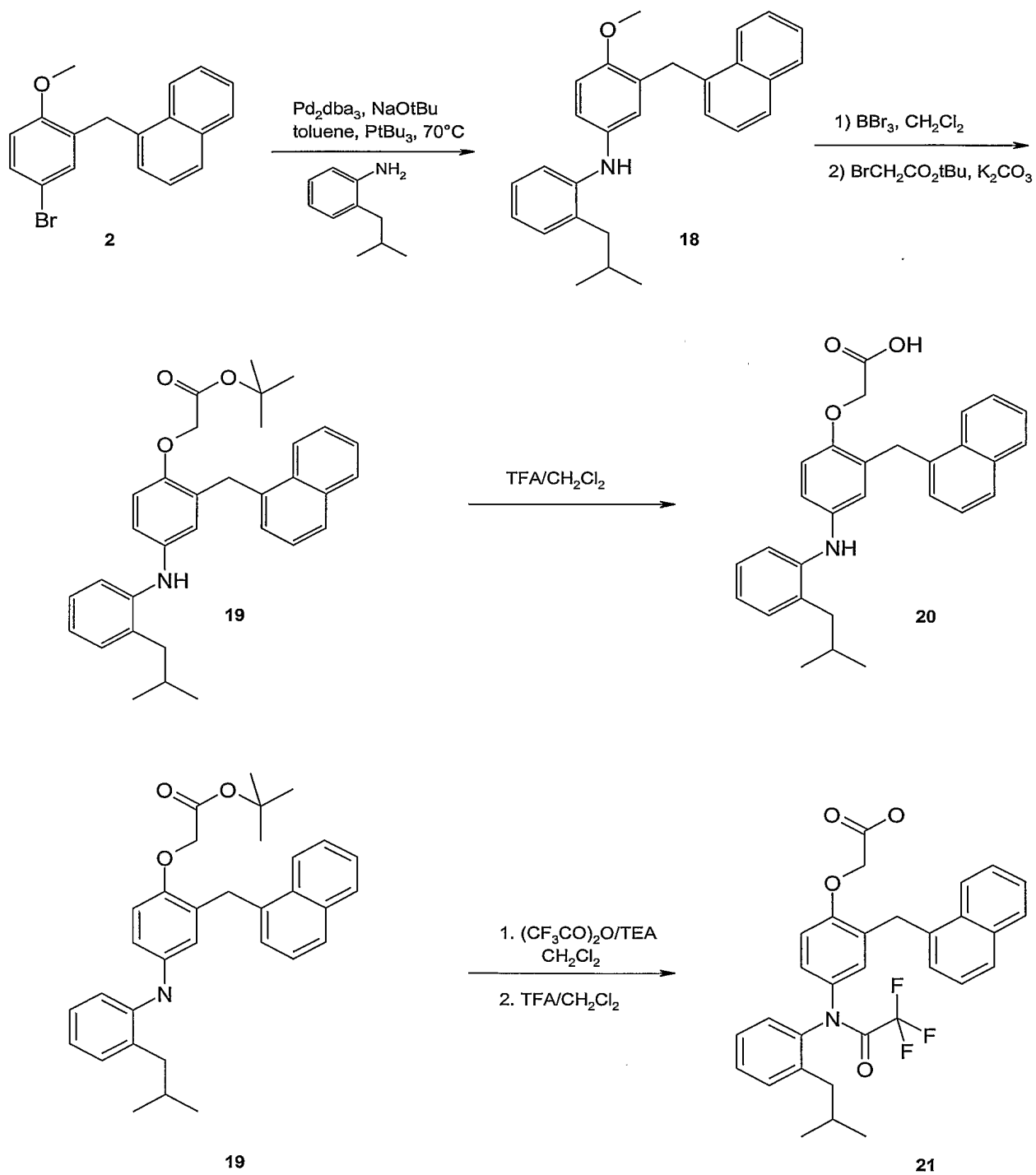
(dd, $J = 7.1, 7.1$ Hz, 1H), 7.17 (m, 3H), 7.38 (dd, $J = 8.1, 7.1$ Hz, 1H), 7.47 (m, 2H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.87 (m, 1H), 8.04 (m, 1H).

[00132] [4-(3,3-Dimethyl-isochroman-1-yl)-2-naphthalen-1-ylmethyl-phenoxy]-acetic acid, 17. To a solution of **16** (7 mg, 0.015 mmol) in 0.5 mL of DCM was added 0.045 mL of a 1 M solution of BBr_3 (3 eqv., 0.045 mmol) in DCM. The solution was allowed to stand at rt for 1 h. The mixture was quenched with H_2O and extracted with DCM. The organic fractions were combined, dried (MgSO_4), filtered, and concentrated in vacuum to yield a crude oil that was used in next step without purification.

[00133] To a mixture of the compound obtained in the previous step (6 mg, 0.015 mmol) and K_2CO_3 (3 eqv., 6 mg, 0.045 mol) in 100 mL of acetone was added *tert*-butyl-bromoacetate (1.05 eqv., 2 μL , 0.015 mmol). The solution was refluxed for 12 h. The solution was allowed to cool to rt, added to H_2O , and extracted with DCM. The organic fractions were combined, dried (MgSO_4), filtered, and concentrated in vacuum to yield a crude oil.

[00134] The *tert*-Butyl ester was dissolved in 0.5 mL of 1:1 TFA/DCM and allowed to stand at room temperature for 12 h. The solution was concentrated in vacuum to yield 4 mg of a white solid (95%). ^1H NMR (400 MHz, CDCl_3) δ 0.55 (s, 3H), 1.09 (s, 3H), 2.68 (c, $J = 4.5$ Hz, 6H), 3.85 (s, 1H), 4.48 (c, $J = 7.0$ Hz, 6H), 4.67 (s, 2H), 6.68 (m, 2H), 6.91 (m, 2H), 7.05 (dd, $J = 7.0, 7.1$ Hz, 1H), 7.17 (m, 3H), 7.41 (dd, $J = 8.0, 7.3$ Hz, 1H), 7.49 (m, 2H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 8.05 (d, $J = 8.0$ Hz, 1H).

EXAMPLE 4



[00135] (2-Isobutyl-phenyl)-(4-methoxy-3-naphthalen-1-ylmethyl-phenyl)-amine, 18. In a 2 dram vial were placed the bromoanisole **2**, (163mg, 0.5 mmol), the alkyl aniline (72 mg, 0.5 mmol), tri-*t*-butylphosphine (90%, 5.0 mg, 0.014 mmol), Pd₂dba₃ (16.3 mg, 0.01 mmol), sodium *t*-butoxide (72 mg, 0.75 mmol) and toluene. The vial was flushed with nitrogen, capped and stirred magnetically at 70°C overnight. The suspension was loaded directly onto a silica gel column and eluted with a 0 to 20% gradient of ethyl acetate in hexanes to afford 93 mg (47%) of the diphenyl amine as a colorless oil. ¹H NMR, 500 MHz, CDCl₃ 8.04-7.98(m, 1H), 7.88-7.83 (m, 1H), 7.737 (d, J=8.337, 1H), 7.477 (ddd, J=4.042, 3.032, 1.011, 1H), 7.453 (ddd, J=4.295, 3.032, 1.263, 1H), 7.389 (dd, J=8.084, 7.074, 1H), 7.251 (d, J=7.074, 1H), 7.07-6.73 (bm, 5H), 6.591 (bs, 1H), 4.392 (s, 2H), 3.863 (bs, 3H), 2.349 (d, J=7.074, 2H), 1.835 (spt, J=6.568, 1H), 0.865 (d, J=6.316, 6H).

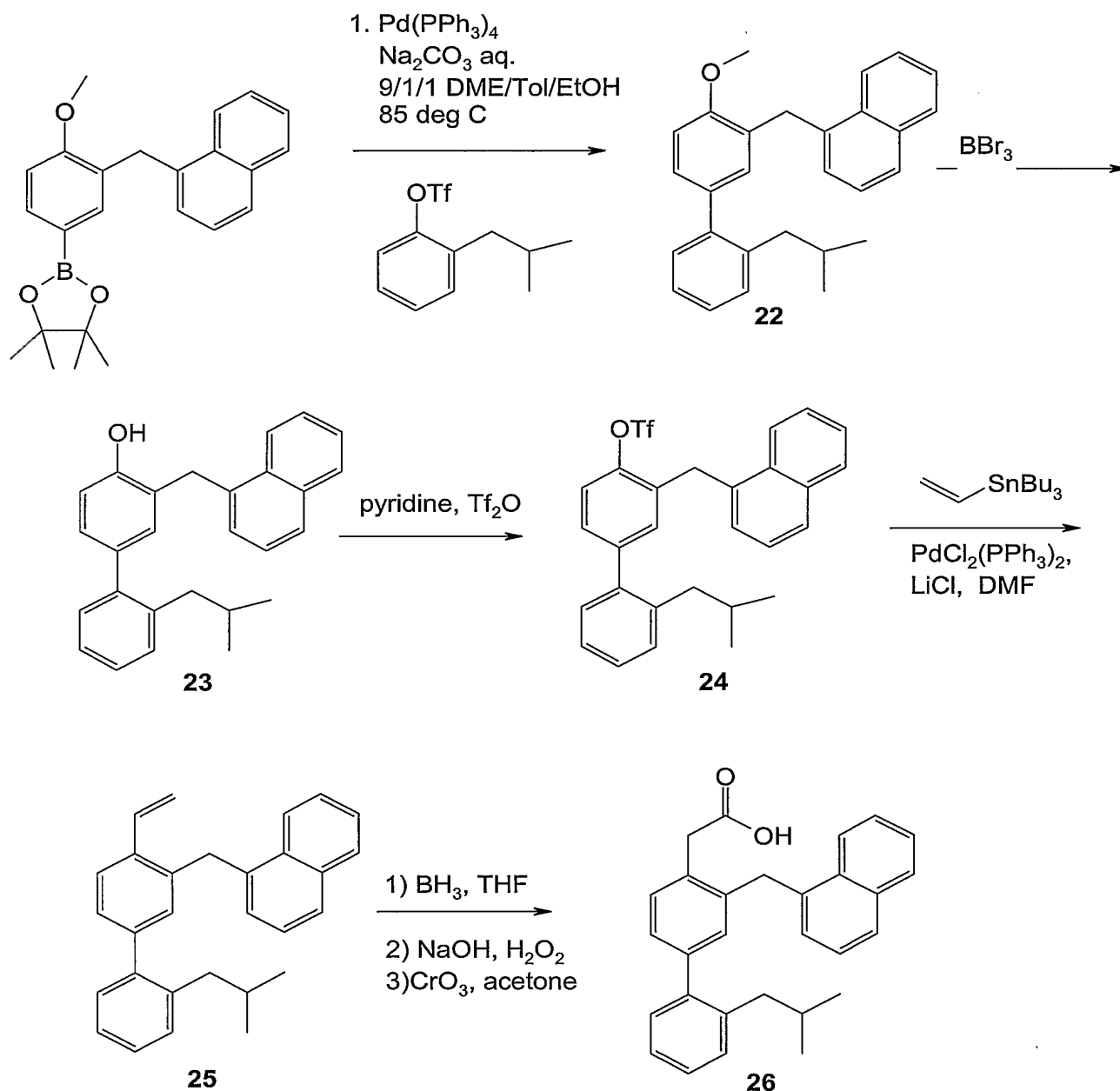
[00136] [4-(2-Isobutyl-phenylamino)-2-naphthalen-1-ylmethyl-phenoxy]-acetic acid tert-butyl ester, 19. In a 2 dram vial were placed the arylaminoanisole **18**, (84 mg, 0.21 mmol) in dichloromethane (0.5 mL). BBr₃ (1M in dichloromethane, 1.0 mL) was added, the vial capped and the solution allowed to sit for 1.5 h. Water was added dropwise until heat evolution subsides. The mixture was partitioned between dichloromethane (5 mL) and water (3 mL). The organic layer was dried over Na₂SO₄. The solvents were removed and the residue dissolved in acetone (3 mL) in a 25 mL round-bottomed flask and treated with *t*-butyl bromoacetate (47 µL, 0.32 mmol) and K₂CO₃ (138 mg, 1 mmol). The reaction was brought to gentle reflux for 3 days after which time the solvents were removed. The residue was suspended in hexane and loaded directly onto a silica gel column and purified, eluting with a gradient from 0 to 10% ethyl acetate/hexane to afford a dark red solid. ¹H NMR (500MHz CDCl₃) 8.029 (dd, J=6.316, 2.779, 1H), 7.86-7.82 (m, 1H), 7.728 (d, J=8.084, 1H), 7.49-7.44 (m, 2H), 7.379 (t, 7.831, 1H), 7.283 (d, J=6.821, 1H), 7.018 (d, J=6.568, 1H), 6.97-6.76 (m, 4H), 6.704 (d, J=7.831, 1H), 6.578 (s, 1H), 4.541 (s, 2H), 4.461 (s, 2H), 2.326 (d, J=7.074, 2H), 1.782 (m, 1H), 1.491 (s, 9H), 0.832 (d, J=5.810, 6H).

[00137] [4-(2-Isobutyl-phenylamino)-2-naphthalen-1-ylmethyl-phenoxy]-acetic acid, 20. In a 2 dram vial were placed the *t*-butyl ester **19** (21.4 mg), followed by 20%

(95%TFA/H₂O)/CH₂Cl₂ at which time the solution turned green. After 45 min sitting at room temperature, the solvent was removed by nitrogen stream. The red solid was purified on silica gel eluting with a gradient from ethyl acetate to 20% methanol/dichloromethane to afford 8.2 mg (42% yield) of a red solid. ¹H NMR (500MHz CDCl₃) 8.018 (d, J=9.600, 1H), 7.87-7.84 (m, 1H), 7.744 (d, J=8.337, 1H), 7.49-7.45 (m, 2H), 7.386 (t, J=8.084, 1H), 7.257 (d, J=8.500, 1H), 7.042 (bs, 1H), 6.958 (bs, 2H), 6.864 (bs, 2H), 6.768 (bs, 1H), 6.609 (bs, 1H), 4.666 (bs 2H), 4.452 (bs, 2H), 2.348 (bs, 2H), 1.809 (spt, J=6.568, 1H), 0.850 (d, J=6.568, 6H); LCMS, (M+H) 439.6.

[00138] **{4-[(2-Isobutyl-phenyl)-(2,2,2-trifluoro-acetyl)-amino]-2-naphthalen-1-ylmethyl-phenoxy}-acetic acid, 21**. The diphenylaniline **19** (15mg, 30μmol) in dichloromethane was treated with trifluoroacetic anhydride (12mg, 60μmol) followed by triethylamine (10 μL, 70μmol). After stirring overnight the solvents were removed and the residue purified on silica gel, eluting with a gradient from 0 to 20% ethyl acetate/hexane to afford 14mg of the trifluoroacetamide. This product was dissolved in dichloromethane (1 mL) and treated with 0.5mL 95%TFA/H₂O for 90 min after which time the solvents were removed and the residue purified on preparative LCMS, affording the final product in 25% yield over 2 steps.

EXAMPLE 5



[00139] **1-(2'-Isobutyl-4-methoxy-biphenyl-3-ylmethyl)-naphthalene, 22.** In a 2 dram vial were placed the pinacol ester, (prepared as described for compound 4), (492 mg, 1.31 mmol), the aryl triflate (483 mg, 1.71 mmol), tetrakis(triphenylphosphine)palladium

(378 mg, 0.33 mmol) and 9:1:1 DME/EtOH/Tol (4.4 mL). 2M Na₂CO₃ (1.31 mL) was added and the vial flushed with nitrogen and then tightly capped. The vial was stirred magnetically at 90°C for 24 h after which time the solvents were removed by nitrogen stream and the residue partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄ and purified on silica gel to afford 356 mg (71% yield) of the biphenyl. ¹H NMR (500MHz, CDCl₃) 8.008 (dd, J=3.537, 6.316, 1H), 7.86-7.81 (m, 1H), 7.718 (d, J=8.337, 1H), 7.47-7.42 (m, 2H), 7.374 (dd, J=7.074, 8.084, 1H), 7.254 (d, J=9.000, 1H), 7.20-7.05 (m, 5H), 6.957 (d, J=8.337, 1H), 6.778 (d, J=2.274, 1H), 4.455 (s, 2H), 3.939 (s, 3H), 2.222 (d, J=7.074, 2H), 1.462 (spt, J=6.821, 1H), 0.541 (d, J=6.568, 6H).

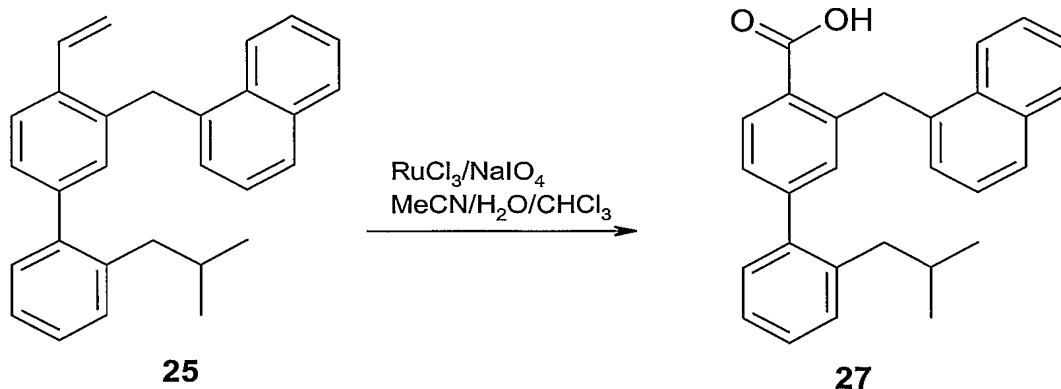
[00140] **2'-Isobutyl-3-naphthalen-1-ylmethyl-biphenyl-4-ol, 23**. In a 40 mL vial were placed the methoxy biphenyl **22** (0.32 g, 0.84 mmol) in CH₂Cl₂ (1 mL). 1M BBr₃ in CH₂Cl₂ (1.60 mL) was added and the vial capped. After 40 min water was added dropwise. The organic layer was separated and dried over Na₂SO₄. The solvents were removed and the residue purified on silica gel, eluting with a gradient from 0-20% ethyl acetate/hexane to afford 214 mg (70%) ¹H NMR (500MHz CDCl₃) 8.09-8.05 (m, 1H), 7.89-7.84 (m, 1H), 7.757 (d, J=8.084, 1H), 7.51-7.46 (m, 2H), 7.396 (dd, 7.074, 8.337, 1H), 7.286 (dd, J=0.758, 7.074, 1H), 7.22-7.094 (m, 4H), 7.045 (dd, J=2.021, 8.084, 1H), 6.918 (d, J=2.021, 1H), 6.867 (d, J=8.084, 1H), 4.477 (s, 2H), 2.314 (d, J=7.326, 2H), 1.525 (spt, J=6.568, 1H), 0.607 (d, J=6.821, 6H).

[00141] **2'-Isobutyl-3-naphthalen-1-ylmethyl-biphenyl-4-ol, 24**. In a 25 mL round-bottomed flask was placed pyridine (3 mL) and biphenol **23** (173 mg, 0.47 mmol) followed by trifluoromethanesulfonic anhydride (168 μL, 1 mmol). After stirring 30 min the solvents were evaporated. The residue was partitioned between water/CH₂Cl₂ and the organic layer dried over Na₂SO₄. The solvents were removed and the residue purified on silica gel, eluting with a gradient from 0-10% ethyl acetate/hexane to afford 88 mg (38% yield) of the triflate as a colorless oil. ¹H NMR(500 MHz, CDCl₃) 7.87-7.79 (m, 2H), 7.773 (d, J=8.337, 1H), 7.48-7.42 (m, 3H), 7.397 (d, J=6.821, 1H), 7.378 (d, J=7.326, 1H), 7.306 (d, J=6.568, 1H), 7.22-7.15 (m, 2H), 7.15-7.06 (m, 2H), 7.000 (dd, J=1.011, 7.326, 1H), 6.800 (d, J=2.021, 1H), 4.556 (s, 2H), 2.080 (d, 7.074, 2H), 1.341 (spt, J=6.821, 1H), 0.466 (d, J=6.568, 6H).

[00142] **1-(2'-Isobutyl-4-vinyl-biphenyl-3-ylmethyl)-naphthalene, 25.** In a 2 dram vial were placed biphenyltriflate **24** (77 mg, 0.154 mmol), tributylvinyltin (68 mL, 0.23 mmol), DMF (1.0 mL), anhydrous LiCl (17.7 mg, 0.40 mmol) and dichlorobis(triphenylphosphine) palladium (12mg, 0.018 mmol). The vial was flushed with nitrogen, capped tightly and heated to 50°C overnight. The reaction mixture was partitioned between water and dichloromethane, the aqueous layer was extracted with dichloromethane (2×) and dried over Na₂SO₄. The solvents were removed and the residue purified on silica gel eluting with a gradient from 0 to 10% ethyl acetate/hexane to afford 55 mg(81%yield) as a colorless amorphous solid. ¹H NMR(500 MHz, CDCl₃) 8.038-8.003 (m, 1H), 7.882-7.854(m, 1H), 7.729(d, J=8.337, 1H), 7.642(d, J=8.084, 1H), 7.506(td, J=6.821, 2.021, 1H), 7.481(dd, J=6.821, 2.021, 1H), 7.348(dd, J=7.074, 8.337, 1H), 7.23-7.11(m, 5H), 7.050(dd, J=1.011, 7.074, 1H), 6.996(dd, J=17.431, 10.863, 1H), 6.993(d, J=1.516, 1H), 5.754(dd, J=1.516, 17.431, 1H), 5.289(dd, J=10.863, 1.263, 1H), 4.532(s, 2H), 2.327(d, J=7.326, 1H), 1.546(spt, J=6.821, 1H), 0.616(d, J=6.821, 6H).

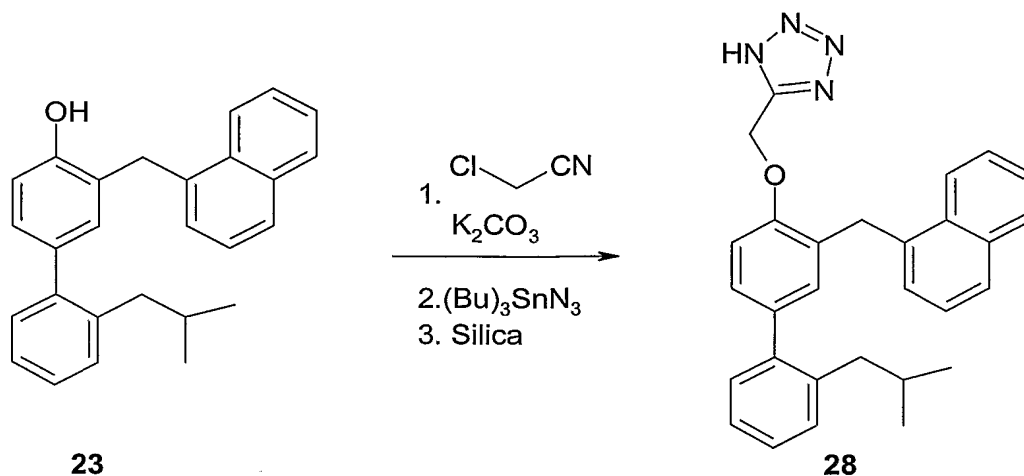
[00143] **(2'-Isobutyl-3-naphthalen-1-ylmethyl-biphenyl-4-yl)-acetic acid, 26.** In a 2 dram vial were placed the biphenyl styrene **25** (28.1mg, 0.075 mmol) and BH₃ as a 1M THF solution (100μL) was added. The solution was stirred for 2 h after which time TLC (1:9 ethyl acetate/hexane) indicated consumption of the starting material. 30% Hydrogen peroxide (100 μL) and 2M NaOH (200 μL) were added. After TLC indicated completion of reaction the solvents were removed and the residue partitioned between dichloromethane and water. The organic layer was dried over Na₂SO₄ and the solvents removed to afford the crude alcohol. The residue was dissolved in acetone and treated with 5 drops of Jones Reagent (4M oxidation equivalent) after which time the solution became deep blue. After 3 h stirring, Jones reagent was added dropwise until the orange color remained for 30 min. Isopropanol was added until the orange color was gone. The solvents were removed and the residue partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2×) and the combined organic layers dried over Na₂SO₄. The solvents were removed and the residue purified on silica gel eluting with a gradient from 0 to 100% ethyl acetate/hexane to afford 10.8 mg (35% yield) of the acid. ¹H NMR (500 MHz, CD₃OD/CD₃COCD₃) 8.007(dd, J=6.821, 2.274, 1H), 7.884(dd, J=7.074, 2.021, 1H), 7.782(d, J=8.084, 1H), 7.49-7.44(m, 2H), 7.43-7.37(m, 2H), 7.233(d,

$J=6.316$, 1H), 7.19-7.07(m, 4H), 7.003(dd, $J=6.316$, 1.768, 1H), 6.698(s, 1H), 4.559(s, 2H), 3.820(s, 2H), 2.215(dd, $J=7.074$, 2.516, 2H), 1.436(spt, $J=5.810$, 1H), 0.527(dd, $J=2.021$, 6.568, 6H).

EXAMPLE 6

[00144] **2'-Isobutyl-3-naphthalen-1-ylmethyl-biphenyl-4-carboxylic acid, 27.** In a 2 dram vial were placed the biphenyl styrene **25** (20 mg, 0.053 mmol), acetonitrile (100 μ L), water (200 μ L), chloroform (100 μ L), ruthenium(III)chloride (6.7mg) and sodium metaperiodate (53 mg, 0.25 mmol). The reaction was stirred overnight after which time the solution was diluted with ethyl acetate (8 mL) and the solution dried over Na_2SO_4 . The solution was filtered, the solvents evaporated and the residue purified on silica gel eluting with a gradient from 0-40% ethyl acetate/hexanes to afford the acid product (6.2 mg, 30% yield). ^1H NMR(500MHz, $\text{CD}_3\text{OD}/\text{CD}_3\text{COCD}_3$) 8.091(d, $J=8.084$, 1H), 8.032 (dd, $J=6.568$, 3.284, 1H), 7.888(dd, $J=3.537$, 5.810, 1H), 7.774 (d, $J=8.337$, 1H), 7.486(t, $J=3.284$, 1H), 7.462(t, $J=3.284$, 1H), 7.402 (dd, $J=7.074$, 8.589, 1H), 7.285 (d, $J=2.021$, 1H), 7.229 (d, $J=2.021$, 1H), 7.201 (dd, $J=1.768$, 7.326, 1H), 7.17-7.12 (m, 2H), 7.030 (dd, $J=1.768$, 7.579, 1H), 6.900 (d, $J=1.768$, 1H), 4.966 (s, 2H), 2.201 (d, $J=7.326$, 2H), 1.386 (spt, $J=6.568$, 1H), 0.498 (d, $J=6.568$, 6H).

EXAMPLE 7



[00145] **5-(2'-Isobutyl-3-naphthalen-1-ylmethyl-biphenyl-4-yloxymethyl)-1H-tetrazole, 28.** To biphenol **23** (0.094 g, 0.26 mmol) in acetone (5 mL) was added chloroacetonitrile (165 μ L, 2.6 mmol, 10 eqv.) and K_2CO_3 (106 mg, 0.77 mmol, 3 eqv.). The mixture was stirred under reflux conditions for 6 hrs., after which the solvent was removed under reduced pressure. The residue was partitioned between DCM and water, the organic layer was washed with brine and dried over Na_2SO_4 . The solvent was evaporated and the crude material was purified by silica gel chromatography, using 0-20% EtOAc/hexanes.

[00146] To the compound obtained in the previous step (71 mg, 0.175 mmol) in 2 mL DME, $(Bu)_3SnN_3$ (0.1 mL, 0.35 mmol, 20 eqv.) was added. The reaction mixture was stirred at 85°C overnight, was allowed to cool to rt and then poured into water. The compound was extracted into DCM, the organic layer was washed with water and dried over Na_2SO_4 . Evaporation yielded the crude product, which was purified by column chromatography, using a hexanes/EtOAc 2/1 mixture.

EXAMPLE 8

Solution for Parenteral Administration

[00147] A solution is prepared from the following ingredients:

Active compound	5 g
Sodium chloride for injection	6 g
Sodium hydroxide for pH adjustment at pH 5-7	
Water for inj.	Up to 1000 mL

[00148] The active constituent and the sodium chloride are dissolved in the water. The pH is adjusted with 2M NaOH to pH 3-9 and the solution is filled into sterile ampoules.

EXAMPLE 9

[00149] Tablets for Oral Administration
1000 tablets are prepared from the following ingredients:

Active compound	100 g
Lactose	200 g
Polyvinyl pyrrolidone	30 g
Microcrystalline cellulose	30 g
Magnesium stearate	6 g

[00150] The active constituent and lactose are mixed with an aqueous solution of polyvinyl pyrrolidone. The mixture is dried and milled to form granules. The microcrystalline cellulose and then the magnesium stearate are then admixed. The mixture is then compressed in a tablet machine giving 1000 tablets, each containing 100 mg of active constituent.

EXAMPLE 10**Inhaler Powder**

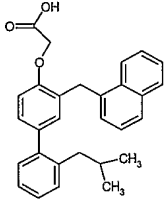
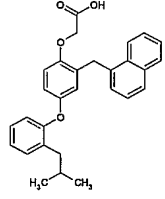
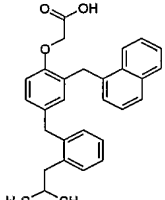
[00151] The active compound is micronized in a jet mill to a particle size suitable for inhalation (mass diameter < 4 μm).

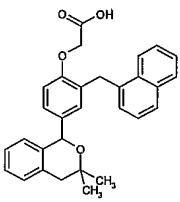
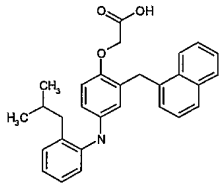
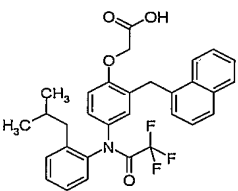
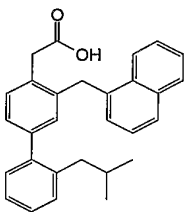
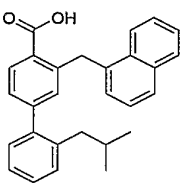
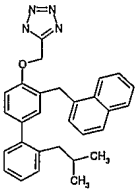
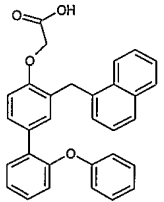
[00152] 100 mg of the micronized powder is filled into a powder multidose inhaler (Turbohaler.RTM.). The inhaler is equipped with a dosing unit which delivers a dose of 1 mg.

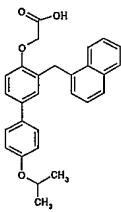
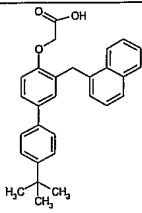
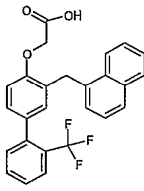
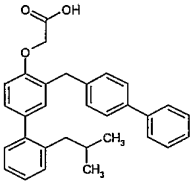
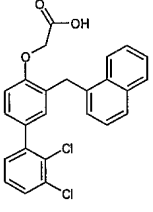
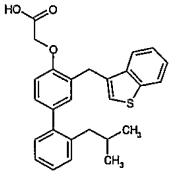
EXAMPLE 11

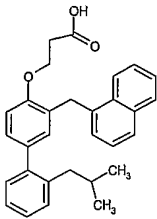
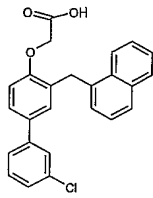
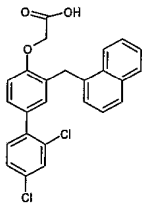
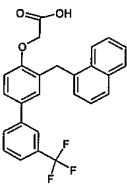
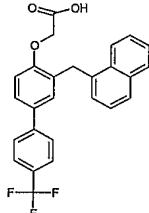
[00153] The compounds in the following Table were synthesized using the methods described above; the structure of each compound was confirmed by ^1H NMR. Each compound also exhibited inhibitory activity in the NC-1 ELISA assay described above.

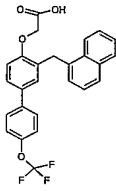
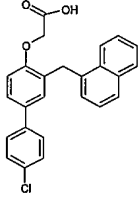
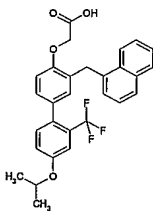
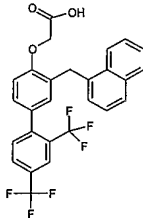
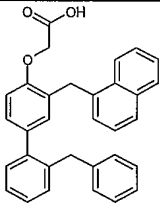
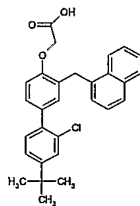
TABLE

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Compound No.	Structure
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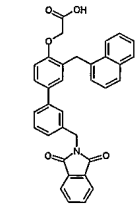
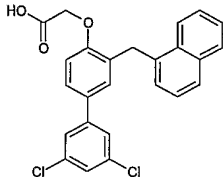
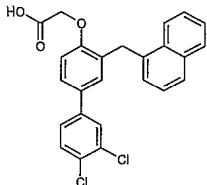
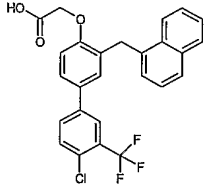
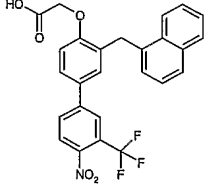
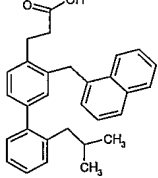
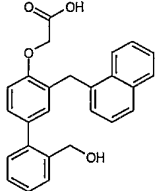
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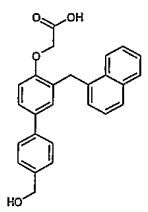
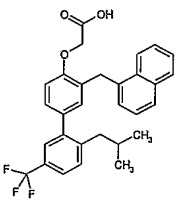
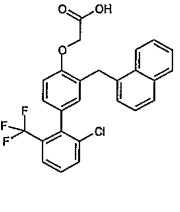
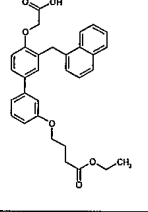
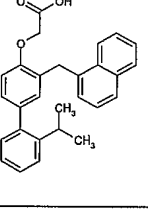
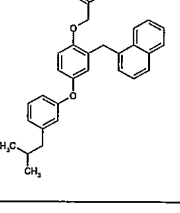
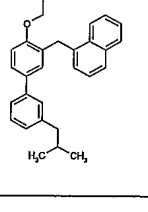
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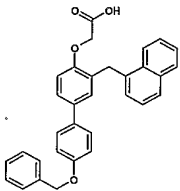
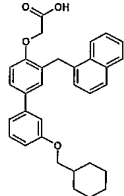
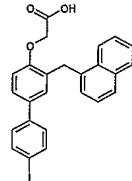
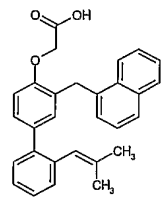
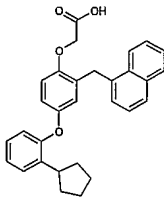
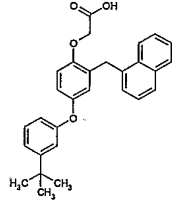
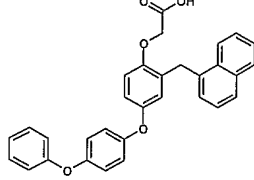
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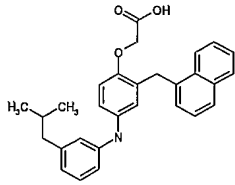
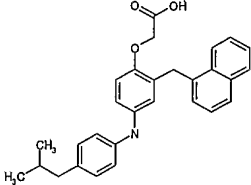
Compound No.	Structure
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52	

Compound No.	Structure
53	<p>Chemical structure of compound 53: A biphenyl system. One phenyl ring is substituted with a carboxylic acid group (-COOH) and a phenoxy group (-O-C₆H₅). The other phenyl ring is unsubstituted.</p>
54	<p>Chemical structure of compound 54: A biphenyl system. One phenyl ring is substituted with a carboxylic acid group (-COOH) and a tert-butyl group (-C(CH₃)₃). The other phenyl ring is unsubstituted.</p>
55	<p>Chemical structure of compound 55: A biphenyl system. One phenyl ring is substituted with a carboxylic acid group (-COOH) and a trifluoromethyl group (-CF₃). The other phenyl ring is unsubstituted.</p>
56	<p>Chemical structure of compound 56: A biphenyl system. One phenyl ring is substituted with a carboxylic acid group (-COOH) and a biphenyl group (-CH₂-C₆H₄-C₆H₅). The other phenyl ring is unsubstituted.</p>
57	<p>Chemical structure of compound 57: A biphenyl system. One phenyl ring is substituted with a carboxylic acid group (-COOH) and a biphenyl group (-CH₂-C₆H₄-C₆H₅). The other phenyl ring is unsubstituted.</p>
58	<p>Chemical structure of compound 58: A biphenyl system. One phenyl ring is substituted with a carboxylic acid group (-COOH), a biphenyl group (-CH₂-C₆H₄-C₆H₅), and a chloromethyl group (-CH₂Cl). The other phenyl ring is unsubstituted.</p>
59	<p>Chemical structure of compound 59: A biphenyl system. One phenyl ring is substituted with a carboxylic acid group (-COOH) and a trifluoromethyl group (-CF₃). The other phenyl ring is unsubstituted.</p>

Compound No.	Structure
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Compound No.	Structure
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Compound No.	Structure
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80	

Compound No.	Structure
81	 <p>Chemical structure of Compound 81: A biphenyl system where one phenyl ring is substituted with a carboxylic acid group (-COOH) and a 4-(4-isobutylphenyl)phenoxy group. The other phenyl ring is substituted with a 4-(4-isobutylphenyl)phenoxy group.</p>
82	 <p>Chemical structure of Compound 82: A biphenyl system where one phenyl ring is substituted with a carboxylic acid group (-COOH) and a 4-(4-isobutylphenyl)phenoxy group. The other phenyl ring is substituted with a 4-(4-isobutylphenyl)phenoxy group.</p>

EXAMPLE 12

[00154] The anti-RSV activity of compounds of this invention is determined using an ELISA for F protein production (Huntley et al. Antimicrobial Agents and Chemotherapy 2002, 841-47). Vero or HFF cells are infected with virus and then incubated with inhibitor at different concentrations for four days. The inhibitory activity is assessed using an antibody to F protein to quantify viral proliferation. Compounds of this invention will be found to display activity in this assay.

EXAMPLE 13

[00155] Inhibition of influenza virus by compounds of the invention may be determined as follows. A viral plaque assay is performed according to the procedure of Kati et al. (Antimicrobial Agents and Chemotherapy 2002, 1014-21). Duplicate MDCK cell monolayers are inoculated with virus. After agitation for 1 hour the virus inoculum is discarded. The cell monolayers are overlaid with DMEM, agarose, trypsin, and inhibitor at different concentrations. After incubation for 72 hours the agar overlay is removed and the cell monolayers are stained. The antiviral efficacy is assessed by measuring the diameters of the plaques. Compounds of this invention will be found to display activity in this assay.

EXAMPLE 14

[00156] Inhibition of ebola virus by compounds of the invention may be determined as follows. A viral plaque assay is performed according to the procedure of Wilson et al. (Science 2000, 287, 1664-66). Inhibitor at varying concentrations is added to Vero cells that have been infected with virus. Cells are overlaid with agarose and incubated for six days. On the sixth day a second overlay is added that contains 5% neutral red. On the following day the plaques are counted. Compounds of this invention will be found to display activity in this assay.

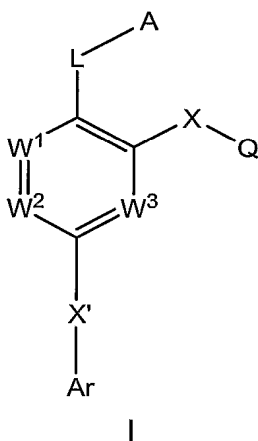
[00157] Having now fully described this invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.

CLAIMS

What is claimed is:

1. A compound having a first planar moiety directly or indirectly attached to an acidic moiety, to a hydrophobic planar moiety, and to a second planar moiety bearing one or more non-aryl and non-heteroaryl substituents.

2. A compound having Formula I:



wherein:

A is hydrogen, OH, NO₂, -COOR, -C(O)NROH, -C(O)CF₃, -B(OH)₂, -SO₃H, -PO₃R₂, -OPO₃R₂, -C(O)NH₂SO₂R, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, OR, CN, NRR, NO₂, R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR;

L is -(CR⁴R⁵)_m-, -O-(CR⁴R⁵)_m-, -S(O)_q-(CR⁴R⁵)_m-, -NR-(CR⁴R⁵)_m-, -NR-C(O)-(CR⁴R⁵)_m-, -C(O)O-(CR⁴R⁵)_m-, -C(O)NR-(CR⁴R⁵)_m-, -NR-C(O)-O-(CR⁴R⁵)_m-, -NR-C(O)NR-(CR⁴R⁵)_m-, -S(O)₂-NR-(CR⁴R⁵)_m-, or -NR-S(O)₂-(CR⁴R⁵)_m-, provided that L and A together are not H, -CH₃, OH, or -OCH₃;

W¹ is N or CR¹;

W² is N or CR²;

W^3 is N or CR^3 ;

X is $-(CR^6R^7)_r-$, $-O-(CR^6R^7)_r-$, $-S(O)_q-(CR^6R^7)_r-$, $-NR-(CR^6R^7)_r-$, $-NR-C(O)-(CR^6R^7)_r-$, $-C(O)O-(CR^6R^7)_r-$, $-C(O)NR-(CR^6R^7)_r-$, $-NR-C(O)-O(CR^6R^7)_r-$, $-NR-C(O)NR-(CR^6R^7)_r-$, $-S(O)_2-NR-(CR^6R^7)_r-$, or $-NR-S(O)_2-(CR^6R^7)_r-$;

X' is a covalent bond, O, $S(O)_q$, NR, $-N(C(O)-R)-$, $-N(C(O)-OR)-$, $-N(C(O)-NRR)-$, $-NR-C(O)-$, $-NR-C(O)-NR-$, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_2 alkenyl, or acetylenyl;

Q is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

Ar is aryl or heterocyclyl, each substituted with one or more R' ;

R at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted $(C_{0-4}$ alkylene)(C_{6-10} aryl), or substituted or unsubstituted $(C_{0-4}$ alkylene)(C_{1-9} heterocyclyl);

R' at each occurrence is independently, F, Cl, Br, I, NO_2 , CN, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted $(C_{1-6}$ alkylene)(C_{6-14} aryl), substituted or unsubstituted $(C_{1-6}$ alkylene)(C_{1-13} heterocyclyl), OR^8 , $-C(O)R^8$, $-COOR^8$, $-S(O)_qR^8$, $-NR^8R^9$, $-C(Y)NR^8R^9$, $-N(R^8)C(Y)OR^9$, $-NR^{10}C(Y)NR^8R^9$, $-NR^{10}C(NR^{11})NR^8R^9$, $-C(NR^{10})NR^8R^9$, $-NR^{10}NR^8R^9$, $-NR^8OR^9$, $-S(O)_qNR^8R^9$, or $-NR^8-SO_2-R^9$, wherein Y is O or S;

R^1 , R^2 , and R^3 , at each occurrence, are independently hydrogen, F, Cl, Br, I, CN, NO_2 , substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted $(C_{0-6}$ alkylene)(C_{6-14} aryl), substituted or unsubstituted $(C_{0-6}$ alkylene)(C_{1-13} heterocyclyl), OR^8 , $-C(O)R^8$, $-COOR^8$, $-S(O)_qR^8$, $-NR^8R^9$, $-C(Y')NR^8R^9$, $-N(R^8)C(Y')OR^9$, $-NR^{10}C(Y')NR^8R^9$, $-NR^{10}C(NR^{11})NR^8R^9$, $-C(NR^{10})NR^8R^9$, $-NR^{10}NR^8R^9$, $-NR^8OR^9$, $-S(O)_qNR^8R^9$, or $-NR^8-SO_2-R^9$, wherein each Y' is independently O or S;

R^4 and R^5 are, at each occurrence, independently hydrogen, F, Cl, Br, I, substituted or unsubstituted straight or branched C_{1-4} alkyl, substituted or unsubstituted C_{2-4} alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, -OR, -COOR -NRR; or R^4 and R^5 , together with the carbon to which they are attached, form a carbonyl;

R^6 and R^7 are, at each occurrence, independently hydrogen, F, Cl, Br, I, substituted or unsubstituted straight or branched C_{1-4} alkyl, substituted or unsubstituted C_{2-4} alkenyl, -OR, -COOR -NRR; or when r is 2 or 3, R^6 and R^7 , together with the carbon to which they are attached, may form a carbonyl;

R^8 , R^9 , R^{10} , and R^{11} , at each occurrence, are independently hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted (C_{0-6} alkylene)(C_{6-10} aryl), or substituted or unsubstituted (C_{0-6} alkylene)(C_{1-9} heterocyclyl); or R^8 and R^9 , together with the N to which they are attached, form a substituted or unsubstituted heterocyclic ring;

$m = 0 - 4$;

each q is independently 0 - 2; and

$r = 0 - 3$;

and stereoisomers thereof, tautomers thereof, solvates thereof, prodrugs thereof, and pharmaceutically acceptable salts thereof;

provided the compound is not acetic acid 3'-(2-acetoxy-4-methoxy-benzoyl)-5-benzoyl-2-methoxy-biphenyl-4-yl ester, acetic acid 5'-(2-acetoxy-4-methoxy-benzoyl)-2,2'-dimethoxy-5-(4-methoxy-benzoyl)-biphenyl-4-yl ester, 5,5'-bis-[bis-(4-tert-butyl-phenyl)-methoxy-methyl]-2,4,2',4'-tetraisopropyl-biphenyl, 3-acetoxy-5-methyl-2-[2,4,2',4'-tetraacetoxy-3'-(2-methoxycarbonyl-4-methyl-6-acetoxybenzoyl)-biphenyl-3-carbonyl]-benzoic acid methyl ester, 3-(3-benzyl-4'-methoxy-biphenyl-4-yl)-propionic acid, 3-(3-benzyl-4'-methoxy-biphenyl-4-yl)-propionyl chloride, or (4,4'-diamino-3'-benzoyl-biphenyl-3-yl)-phenyl-methanone.

3. The compound of claim 2, wherein A is OH, NO₂, -COOR, -C(O)NROH, -C(O)CF₃, -B(OH)₂, -SO₃H, -PO₃H₂, -OPO₃H₂, -C(O)NH₂SO₂R, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, OR, CN, NRR, NO₂, R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR.

4. The compound of claim 2, wherein A is hydrogen, -COOR, -C(O)NROH, -C(O)CF₃, -B(OH)₂, -SO₃H, -PO₃H₂, -OPO₃H₂, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, OR, CN, NRR, NO₂, R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR.

5. The compound of claim 2, wherein A is substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, OR, CN, NRR, NO₂, R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR.

6. The compound of claim 2, wherein A is -COOR, -C(O)NHOH, -C(O)CF₃, or -B(OH)₂.

7. The compound of claim 2, wherein A is -COOR.

8. The compound of claim 2, wherein A is -COOH.

9. The compound of claim 2, wherein L is -(CR⁴R⁵)_m-, -O-(CR⁴R⁵)_m-, -S(O)_q-(CR⁴R⁵)_m-, -NR-(CR⁴R⁵)_m-, -C(O)O-(CR⁴R⁵)_m-, -C(O)NR-(CR⁴R⁵)_m-, -NR-C(O)-O-(CR⁴R⁵)_m-, or -NR-C(O)NR-(CR⁴R⁵)_m-.

10. The compound of claim 2, wherein L is -(CR⁴R⁵)_m-, -O-(CR⁴R⁵)_m-, -S(O)_q-(CR⁴R⁵)_m-, -NR-(CR⁴R⁵)_m-, -NR-C(O)-(CR⁴R⁵)_m-, -C(O)O-(CR⁴R⁵)_m-, or -C(O)NR-(CR⁴R⁵)_m-.

11. The compound of claim 2, wherein L is -(CR⁴R⁵)_m-, -O-(CR⁴R⁵)_m-, -S(O)_q-(CR⁴R⁵)_m-, or -NR-(CR⁴R⁵)_m-.

12. The compound of claim 2, wherein L is $-(CR^4R^5)_m-$ or $-O-(CR^4R^5)_m-$.
13. The compound of claim 2, wherein L is $-O-(CR^4R^5)_m-$.
14. The compound of claim 13, wherein R^4 and R^5 are each hydrogen.
15. The compound of claim 13, wherein $m = 1-2$.
16. The compound of claim 2, wherein L and A together are $-(CR^4R^5)_m-COOR$ or $-O-(CR^4R^5)_m-COOR$.
17. The compound of claim 2 wherein R^4 and R^5 are, at each occurrence, independently hydrogen, F, Cl, Br, I, substituted or unsubstituted straight or branched C_{1-4} alkyl, substituted or unsubstituted C_{2-4} alkenyl, OR, COOR, or -NRR; or R^4 and R^5 , together with the carbon to which they are attached, form a carbonyl.
18. The compound of claim 2, wherein $m = 1-3$.
19. The compound of claim 2, wherein X is $-(CR^6R^7)_r-$, $-O-(CR^6R^7)_r-$, $-S(O)_q-(CR^6R^7)_r-$, $-NR-(CR^6R^7)_r-$, $-NR-C(O)-(CR^6R^7)_r-$, $-C(O)O-(CR^6R^7)_r-$, $-C(O)NR-(CR^6R^7)_r-$, $-NR-C(O)-O(CR^6R^7)_r-$, or $-NR-C(O)NR-(CR^6R^7)_r-$.
20. The compound of claim 2, wherein X is $-(CR^6R^7)_r-$, $-O-(CR^6R^7)_r-$, $-S(O)_q-(CR^6R^7)_r-$, $-NR-(CR^6R^7)_r-$, $-C(O)O-(CR^6R^7)_r-$, or $-C(O)NR-(CR^6R^7)_r-$.
21. The compound of claim 2, wherein X is $-(CR^6R^7)_r-$, $-O-(CR^6R^7)_r-$, or $-S(O)_q-(CR^6R^7)_r-$.
22. The compound of claim 2, wherein X is $-(CR^6R^7)_r-$.
23. The compound of claim 22, wherein X is $-CH_2-$.
24. The compound of claim 2, wherein Q is a substituted or unsubstituted cycloalkyl or substituted or unsubstituted cycloalkenyl.

25. The compound of claim 2, wherein Q is a substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclalkyl.
26. The compound of claim 2, wherein Q is a substituted or unsubstituted aryl or substituted or unsubstituted aralkyl.
27. The compound of claim 2, wherein Q is a fused or unfused bicyclic ring selected from the group consisting of substituted and unsubstituted C₉₋₁₂ aryl, substituted and unsubstituted C₇₋₁₂ cycloalkyl, substituted and unsubstituted C₉₋₁₂ cycloalkenyl, and substituted and unsubstituted C₇₋₁₂ heterocyclyl.
28. The compound of claim 2, wherein Q is a fused or unfused bicyclic ring that is substituted or unsubstituted C₉₋₁₂ aryl.
29. The compound of claim 2, wherein Q is substituted or unsubstituted 1-naphthyl, 2-naphthyl, or 4-biphenyl.
30. The compound of claim 29, wherein X is -CH₂-.
31. The compound of claim 2 wherein X' is a covalent bond, O, S(O)_q, -NR-, -NR-C(O)-, -NR-C(O)-NR-, substituted or unsubstituted C₁₋₂ alkyl, substituted or unsubstituted C₂ alkenyl, or acetylenyl.
32. The compound of claim 2 wherein X' is a covalent bond, O, S(O)_q, or -NR-.
33. The compound of claim 2 wherein X' is a substituted or unsubstituted C₁₋₂ alkyl.
34. The compound of claim 2 wherein X' is a covalent bond.
35. The compound of claim 2 wherein X' is -N(C(O)-R)-, -N(C(O)-OR)-, or -N(C(O)-NRR)-.
36. The compound of claim 2, wherein W¹ is CR¹.

37. The compound of claim 2, wherein W^2 is CR^2 .
38. The compound of claim 2, wherein W^3 is CR^3 .
39. The compound of claim 2, wherein W^1 is CR^1 , W^2 is CR^2 , and W^3 is CR^3 .
40. The compound of claim 2, wherein W^1 is N, W^2 is N, and W^3 is CR^3 .
41. The compound of claim 2, wherein W^1 is CR^1 , W^2 is N, and W^3 is N.
42. The compound of claim 2, wherein Ar is a 6-member aryl, a 5- or 6-member heteroaryl, a 9-12 member bicyclic aryl or heterocyclyl, each substituted with one or more R' .
43. The compound of claim 2, wherein Ar is a 6-member aryl or a 5-, or 6-member heteroaryl, each substituted with one or more R' .
44. The compound of claim 2, wherein Ar is a 9-12 member bicyclic aryl or heterocyclyl, each substituted with one or more R' .
45. The compound of claim 2, wherein Ar is 6-member aryl, substituted with one or more R' .
46. The compound of claim 2, wherein Ar is a 5- or 6-member heteroaryl, substituted with one or more R' .
47. The compound of claim 2, wherein Ar is substituted with one or more R' and is selected from the group consisting of phenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thiophenyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

48. The compound of claim 2, wherein Ar is substituted with one or more R' and is selected from the group consisting of phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thiophenyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl.

49. The compound of claim 2, wherein Ar is substituted with one or more R' and is selected from naphthyl, indolyl, benzofuranyl, benzthiazolyl, benzothiophenyl, chromanyl, isochromanyl, or coumarinyl.

50. The compound of claim 2, wherein Ar is phenyl substituted with one or more R'.

51. The compound of claim 2, wherein R¹, R², and R³, at each occurrence, are independently hydrogen, F, Cl, Br, I, CN, NO₂, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₂₋₈ alkenyl, substituted or unsubstituted (C₀₋₆ alkylene)(C₆₋₁₄ aryl), substituted or unsubstituted (C₀₋₆ alkylene)(C₁₋₁₃ heterocyclyl), -OR⁸, -C(O)R⁸, -COOR⁸, -S(O)_qR⁸, -NR⁸R⁹, -C(O)NR⁸R⁹, -N(R⁸)C(O)OR⁹, -NR¹⁰C(O)NR⁸R⁹, -NR¹⁰C(NR¹¹)NR⁸R⁹, -C(NR¹⁰)NR⁸R⁹, -NR¹⁰NR⁸R⁹, -NR⁸OR⁹, -S(O)_qNR⁸R⁹, or -NR⁸-SO₂-R⁹.

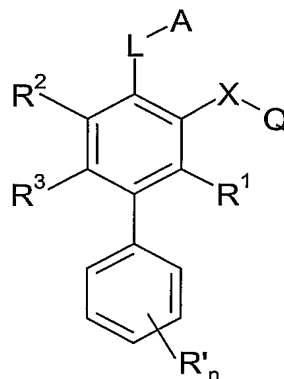
52. The compound of claim 2, wherein R', at each occurrence, is independently F, Cl, Br, I, CN, NO₂, substituted or unsubstituted C₁₋₈ alkyl, substituted or unsubstituted C₂₋₈ alkenyl, substituted or unsubstituted (C₁₋₆ alkylene)(C₆₋₁₄ aryl), substituted or unsubstituted (C₁₋₆ alkylene)(C₁₋₁₃ heterocyclyl), -OR⁸, -C(O)R⁸, -COOR⁸, -NR⁸R⁹, -C(Y)NR⁸R⁹, or -N(R⁸)C(Y)OR⁹, wherein Y is O or S.

53. The compound of claim 2 wherein R', at each occurrence, is independently F, Cl, Br, I, NO₂, substituted or unsubstituted C₁₋₈ alkyl, substituted or unsubstituted C₂₋₈ alkenyl, OR⁸, or -COOR⁸.

54. The compound of claim 2, wherein R⁸ and R⁹, together with the nitrogen to which they are attached, form a substituted or unsubstituted heterocyclyl.

55. The compound of claim 54, wherein the heterocyclyl is selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and pyrazinyl.

56. The compound of claim 2 having Formula V



(V)

wherein $n = 1-5$.

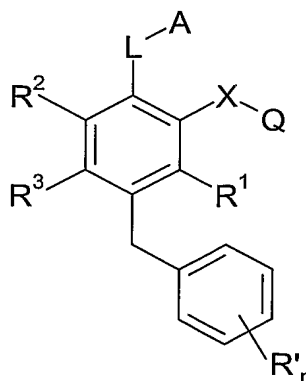
57. The compound of claim 56 wherein A is hydrogen, $-\text{COOR}$, $-\text{C(O)NROH}$, $-\text{C(O)CF}_3$, $-\text{B(OH)}_2$, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, $-\text{OR}$, $-\text{CN}$, $-\text{NRR}$, $-\text{NO}_2$, $-\text{R}$, $-\text{COOR}$, $-\text{C(O)NRR}$, $-\text{OC(O)R}$, $-\text{NRC(O)R}$, $-\text{OC(O)NR}$, and $-\text{NRC(O)OR}$.

58. The compound of claim 56, wherein L is $-(\text{CR}^4\text{R}^5)_m$, $-\text{O}-(\text{CR}^4\text{R}^5)_m$, $-\text{S(O)}_q-(\text{CR}^4\text{R}^5)_m$, $-\text{NR}-(\text{CR}^4\text{R}^5)_m$, $-\text{NR}-\text{C(O)}-(\text{CR}^4\text{R}^5)_m$, $-\text{C(O)O}-(\text{CR}^4\text{R}^5)_m$, $-\text{C(O)NR}-(\text{CR}^4\text{R}^5)_m$, $-\text{NR}-\text{C(O)}-\text{O}-(\text{CR}^4\text{R}^5)_m$, or $-\text{NR}-\text{C(O)NR}-(\text{CR}^4\text{R}^5)_m$.

59. The compound of claim 56, wherein L is $-(\text{CR}^4\text{R}^5)_m$ or $-\text{O}-(\text{CR}^4\text{R}^5)_m$.

60. The compound of claim 56, wherein L and A together are $-(\text{CR}^4\text{R}^5)_m-\text{COOR}$ or $-\text{O}-(\text{CR}^4\text{R}^5)_m-\text{COOR}$.

61. The compound of claim 2 having Formula VI



(VI)

wherein n = 1 – 5.

62. The compound of claim 61 wherein A is hydrogen, -COOR, -C(O)NROH, -C(O)CF₃, -B(OH)₂, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, -OR, -CN, -NRR, -NO₂, -R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR.

63. The compound of claim 61, wherein L is -(CR⁴R⁵)_m-, -O-(CR⁴R⁵)_m-, -S(O)_q-(CR⁴R⁵)_m-, -NR-(CR⁴R⁵)_m-, -NR-C(O)-(CR⁴R⁵)_m-, -C(O)O-(CR⁴R⁵)_m-, -C(O)NR-(CR⁴R⁵)_m-, -NR-C(O)-O(CR⁴R⁵)_m-, or -NR-C(O)NR-(CR⁴R⁵)_m-.

64. The compound of claim 61, wherein L is -(CR⁴R⁵)_m- or -O-(CR⁴R⁵)_m-.

65. The compound of claim 61, wherein L and A together are -(CR⁴R⁵)_m-COOR or -O-(CR⁴R⁵)_m-COOR.

66. A pharmaceutical composition, comprising a pharmaceutically effective amount of the compound of claim 2 and a pharmaceutically acceptable carrier or diluent.

67. A method for the treatment of viral infection, the method comprising administering the composition of claim 66 to a subject in need thereof.

68. The method of claim 67, wherein the viral infection is HIV, ebola, HRSV, or influenza infection.

69. The method of claim 67, wherein the viral infection is HIV

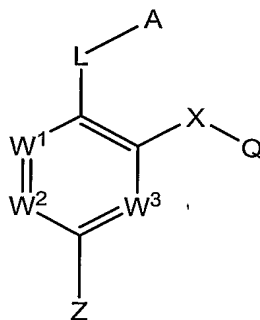
70. A method for the inhibition of cell entry by a virus, the method comprising contacting a virus with a compound of claim 2.

71. The method of claim 70, wherein the virus is HIV, ebola, HRSV, or influenza.

72. The method of claim 70, wherein the virus is HIV.

73. A method of preparing a compound of claim 2 wherein X' is a covalent bond or NH, the method comprising

reacting a compound of Formula III



(III)

with a compound of Formula IV



(IV)

in the presence of a palladium catalyst, a base, and a solvent

to form a compound of claim 2 wherein X' is a covalent bond or NH, and wherein

A, Ar, L, X, Q, Z, W¹, W², and W³ are as defined in claim 2;

Z is B(OR'')₂ or NH₂, and Z' is I, Br, Cl, or OTf; or

Z is I, Br, Cl, or OTf, and Z' is B(OR'')₂ or NH₂; and

wherein each R'' is independently hydrogen or substituted or unsubstituted alkyl, or, each R'', together with B and the atoms to which they are attached, form a cyclic boronate.

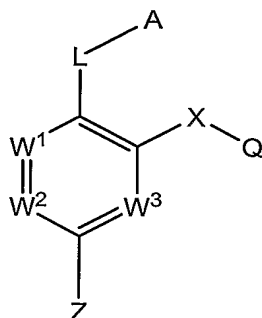
74. The method of claim 73, wherein the palladium catalyst is Pd₂(dba)₃ or Pd(PPh₃)₄.

75. The method of claim 73, wherein the base is Na₂CO₃, K₂CO₃, or NaOtBu.

76. The method of claim 73, wherein the solvent is DMF, toluene, or a mixture of DME, ethanol and toluene.

77. A method of preparing a compound of claim 2 wherein X' is O, the method comprising

reacting a compound of Formula III



(III)

with a compound of Formula IV



(IV)

in the presence of a copper catalyst, a base, and a solvent

to form a compound of claim 2 wherein X' is O, and wherein

A, Ar, L, X, Q, Z, W¹, W², and W³ are as defined in claim 2;

Z is OH, and Z' is I, Br, Cl, or OTf; or Z is I, Br, Cl, or OTf, and Z' is OH.

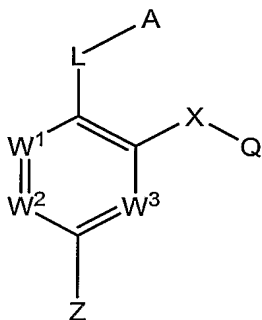
78. The method of claim 77, wherein the copper catalyst is CuI.

79. The method of claim 77, wherein the base is Cs₂CO₃.

80. The method of claim 77, wherein the solvent is toluene.

81. A method of preparing a compound of claim 2 wherein X' is –CH(OH)-, the method comprising

reacting a compound of Formula III



(III)

with a compound of Formula IV



(IV)

in the presence of a solvent

to form a compound of claim 2 wherein X' is –CH(OH)-, and

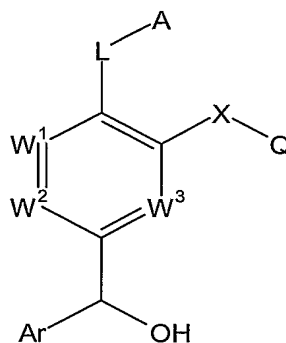
wherein

A, Ar, L, X, Q, W¹, W², and W³ are as defined in claim 2;

Z is Li, and Z' is C(O)-H; or Z is C(O)-H, and Z' is Li.

82. The method of claim 81, wherein the solvent is THF or diethylether.

83. A method of preparing a compound of claim 2, wherein X' is $-\text{CH}_2-$, the method comprising treating a compound having Formula VII



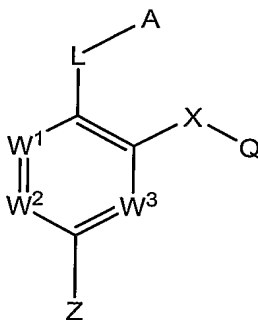
(VII)

with a reducing agent in a solvent.

84. The method of claim 83 where the reducing agent is H₂ in the presence of Pd/C or triethylsilane with trifluoroacetic acid.

85. The method of claim 83, where the solvent is EtOAc or DCM.

86. An intermediate having the Formula III:



(III)

wherein,

A is hydrogen, OH, NO₂, -COOR, -C(O)NROH, -C(O)CF₃, -B(OH)₂, -SO₃H, -PO₃R₂, -OPO₃R₂, -C(O)NHSO₂R, or substituted or unsubstituted tetrazole, triazole, thiazole, oxazole, isoxazole, imidazole, or pyrazole, wherein the substituents are selected from the group consisting of F, Cl, Br, I, -OR, -CN, -NRR, -NO₂, -R, -COOR, -C(O)NRR, -OC(O)R, -NRC(O)R, -OC(O)NR, and -NRC(O)OR;

L is -(CR⁴R⁵)_m-, -O-(CR⁴R⁵)_m-, -S(O)_q-(CR⁴R⁵)_m-, -NR-(CR⁴R⁵)_m-, -C(O)O-(CR⁴R⁵)_m-, -C(O)NR-(CR⁴R⁵)_m-, -NR-C(O)-O(CR⁴R⁵)_m-, -NR-C(O)NR-(CR⁴R⁵)_m-, -S(O)₂-NR-(CR⁴R⁵)_m-, or -NR-S(O)₂-(CR⁴R⁵)_m-;

W¹ is N or CR¹;

W² is N or CR²;

W³ is N or CR³;

X is -(CR⁶R⁷)_r-, -O-(CR⁶R⁷)_r-, -S(O)_q-(CR⁶R⁷)_r-, -NR-(CR⁶R⁷)_r-, -C(O)O-(CR⁶R⁷)_r-, -C(O)NR-(CR⁶R⁷)_r-, -NR-C(O)-O(CR⁶R⁷)_r-, -NR-C(O)NR-(CR⁶R⁷)_r-, -S(O)₂-NR-(CR⁶R⁷)_r-, or -NR-S(O)₂-(CR⁶R⁷)_r-;

Q is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

Z is B(OR'')₂, NH₂, OH, I, Br, Cl, C(O)-H, Li or OTf;

wherein each R'' is independently hydrogen or substituted or unsubstituted alkyl, or, each R'' together with B and the atoms to which they are attached, form a cyclic boronate;

R at each occurrence is independently hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted (C₀₋₄ alkylene)(C₆₋₁₀ aryl), or substituted or unsubstituted (C₀₋₄ alkylene)(C₁₋₉ heterocyclyl);

m = 0 - 4;

each q is independently 0 - 2;

r = 0 - 3;

and stereoisomers thereof, tautomers thereof, and solvates thereof.

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(54) Title: COMPOUNDS FOR THE TREATMENT OF VIRAL INFECTION

(57) Abstract: The present invention is related to compounds, their intermediates, processes for their preparation and use, and phar-
maceutical compositions comprising the compounds. The novel compounds are useful in therapy, and in particular for the treatment
of viral infection, particularly HIV infection.



WO 2004/071426 A3

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International application No.

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Cas-online search: structural search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	Kutzki et al Develment of a Potent Bcl-x Antagonist Based on a-Helix Mimicry, J. of the American Chemical Society. 2002, 124(40), pages 11838-11839.	1-23,25-32,34, 36-39, 42-45, 47-52,56-66 ----- 24,, 33, 35, 40-41, 46,, 53-55, 67-86

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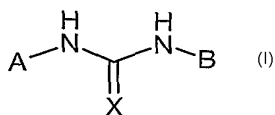
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** POSITIVE ALLOSTERIC MODULATORS OF THE NICOTINIC ACETYLCHOLINE RECEPTOR



(57) **Abstract:** The invention provides compounds of Formula (I). These compounds may be in the form of pharmaceutical salts or compositions, may be in pure enantiomeric form or racemic mixtures, and are useful in pharmaceuticals used to treat diseases or conditions in which $\alpha 7$ nAChR is known to be involved.



WO 2004/085433 A2

POSITIVE ALLOSTERIC MODULATORS OF THE NICOTINIC ACETYLCHOLINE RECEPTOR

5 FIELD OF INVENTION

This invention relates to the use of certain urea and thiourea compounds as positive allosteric modulators of nicotinic acetylcholine receptors. It also relates to novel urea and thiourea compounds and to pharmaceutical compositions containing them.

10

BACKGROUND OF THE INVENTION

Nicotinic acetylcholine receptors (nAChRs) play a large role in central nervous system (CNS) activity and in different tissue throughout the body. They are known to be involved in functions, including, but not limited to, cognition, learning, mood,
15 emotion, and neuroprotection. There are several types of nicotinic acetylcholine receptors, and each one appears to have a different role. Some nicotinic receptors regulate CNS function, including, but not limited to, attention, learning and memory; some regulate pain, inflammation, cancer, and diabetes by controlling tumor necrosis factor alpha (TNF- α); and some regulate vascular angiogenesis; for example, the
20 binding of nicotine to the α 7 nAChR stimulates DNA synthesis and proliferation of vascular endothelial cells *in vitro* (Villablanca, A.C., 1998, *J. Appl. Physiol.*, 84(6):2089-2098) and induces angiogenesis *in vivo* (Heeschen C., et al. 2002, *J. Clin. Invest.*, 110:527-535; Heeschen, C., et al. 2001, *Nature Medicine*, 7(7): 833-839). Nicotine affects all such receptors, and has a variety of activities. Unfortunately, not
25 all of the activities are desirable. In fact, undesirable properties of nicotine include its addictive nature and the low ratio between efficacy and safety. The compounds of the present invention activate the α 7 nAChR by acting as positive allosteric modulators (PAMs) of this ion channel. These molecules activate the α 7 nAChR to enhance the activity of agonists at this receptor, including, but not limited to, acetylcholine (ACh)
30 that is the endogenous neurotransmitter that activates this receptor.

Cell surface receptors are, in general, excellent and validated drug targets. nAChRs comprise a large family of ligand-gated ion channels that control neuronal activity and brain function. These receptors have a pentameric structure. In

mammals, this gene family is composed of nine alpha and four beta subunits that co-assemble to form multiple subtypes of receptors that have a distinctive pharmacology. Acetylcholine is the endogenous regulator of all of the subtypes, while nicotine non-selectively activates all nAChRs.

5 The $\alpha 7$ nAChR is one receptor system that has proved to be a difficult target for testing. Native $\alpha 7$ nAChR is not routinely able to be stably expressed in most mammalian cell lines (Cooper and Millar, *J. Neurochem.*, 1997, 68(5):2140-51). Another feature that makes functional assays of $\alpha 7$ nAChR challenging is that the receptor is rapidly (100 milliseconds) inactivated. This rapid inactivation greatly
10 limits the functional assays that can be used to measure channel activity.

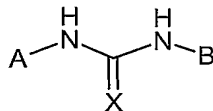
 Both agonist and positive allosteric modulator activity of the $\alpha 7$ nAChR are assayed using a cell-based, calcium flux assay on FLIPR. SHEP-1 cells expressing a novel, mutated form of the $\alpha 7$ nAChR that permitted stable cell surface expression were used for these assays. The details of the mutated form of the $\alpha 7$ nAChR are
15 described in WO 00/73431.

 A positive allosteric modulator of $\alpha 7$ nAChR will effectively activate the endogenous $\alpha 7$ nAChR if there is sufficient agonist in the brain and elsewhere within the body to at least partially stimulate this receptor. Therefore, a positive allosteric modulator of $\alpha 7$ nAChR can be administered alone to treat CNS diseases or
20 conditions as discussed herein. In certain diseases, however, it is possible that the full therapeutic efficacy of a positive allosteric modulator of $\alpha 7$ nAChR will be limited by suboptimal levels of agonist which in turn leads to a suboptimal activation of the endogenous $\alpha 7$ nAChR in the presence of a positive allosteric modulator. In such cases, the positive allosteric modulator of $\alpha 7$ nAChR is administered in combination
25 with another agent that affects the level of agonist.

 The activation of the $\alpha 7$ nAChR is also useful to treat, or used to prepare a medicament used to treat, diseases or conditions where a mammal receives symptomatic relief from the decrease of levels of TNF- α . The compounds of the present invention are useful to treat, or are used to prepare a medicament to treat,
30 diseases or conditions where a mammal receives symptomatic relief from the stimulation of vascular angiogenesis.

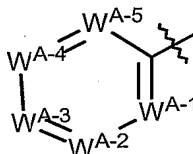
SUMMARY OF THE INVENTION

The present invention discloses compounds of the Formula I:



wherein X is O or S;

5 A is



wherein each W^{A-1} , W^{A-2} , W^{A-3} , W^{A-4} , and W^{A-5} are independently N or CR_A , provided that no more than four of W^{A-1} , W^{A-2} , W^{A-3} , W^{A-4} , or W^{A-5} are simultaneously N;

10 Each R_A is R_{A-1} or R_{A-2} , provided that one R_A is R_{A-2} ;

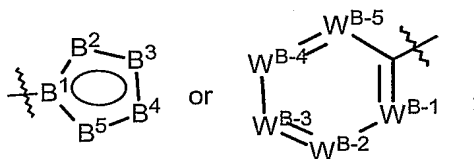
Each R_{A-1} is independently H, halogen, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, aryl, $-N_3$, $-SCN$, $-CN$, $-NO_2$, $-OR_7$, $-SR_8$,
15 $-S(O)R_8$, $-S(O)_2R_8$, $-N(R_9)_2$, $-C(O)R_{10}$, $-C(O)OR_7$, $-C(O)N(R_9)_2$, $-NR_9C(O)R_{10}$, $-C(R_{10})=NOR_7$, $-S(O)_2N(R_9)_2$, $-NR_9S(O)_2R_8$, $-N(R_9)C(O)N(R_9)_2$;

R_{A-2} is R_1 , R_2 , OR_1 , OR_2 , $N(R_{A-3})R_1$, $N(R_{A-3})R_2$, SR_1 , and SR_2 ;

R_{A-3} is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl,
20 substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

B is a five or six-membered aromatic ring having up to 4 heteroatoms selected from $-O-$, $-N(R_{B-3})-$, $=N-$, or $-S-$;

wherein B is



25

B^1 is N, or C;

B^2 , B^3 , B^4 , and B^5 are independently N, O, S, C, provided that when valency allows, the N can have a third bond to R_{B-3} , and further provided that when valency allows, the C can have a fourth bond to R_{B-1} ;

Each R_{B-1} is independently H, halogen, alkyl, haloalkyl, substituted alkyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, aryl, -CN, -N₃, -NO₂, -COR₁₀, -CO₂R₇, -CON(R₉)₂, -C(R₁₀)=NOR₇, -SCN, -OR₇, -N(R₉)₂, -SR₈, -SOR₈, -SO₂R₈, -SN(R₉)₂, -SON(R₉)₂, -SO₂N(R₉)₂; or

when two R_{B-1} are on adjacent carbon atoms, the two R_{B-1} may combine to form a 5-7-membered ring fused to the 5 or 6 membered ring giving a fused-bicyclic-ring system; wherein the 5-7-membered ring is saturated or unsaturated having up to two heteroatoms selected from -O-, -S-, -N(R_{B-3})-, or -N= and further having substitution where valency allows on the 5-7-membered ring with up to 2 substituents independently selected from R_{B-2} ;

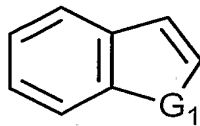
Each R_{B-2} is independently H, F, Cl, Br, I, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, haloalkyl, haloalkenyl, haloalkynyl, halocycloalkyl, haloheterocycloalkyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, -CN, -NO₂, -OR₇, -SR₈, -S(O)₂R₈, -S(O)R₈, -OS(O)₂R₈, -N(R₉)₂, -C(O)R₁₀, -C(S)R₁₀, -C(O)₂R₇, -C(O)N(R₉)₂, -NR₉C(O)R₁₀, -S(O)₂N(R₉)₂, -NR₉S(O)₂R₈, -N(R₉)C(O)N(R₉)₂, or aryl;

R_{B-3} is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

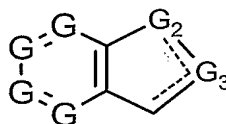
Each W^{B-1} , W^{B-2} , W^{B-3} , W^{B-4} , and W^{B-5} are independently N or CR_{B-1}, provided that no more than 4 of W^{B-1} , W^{B-2} , W^{B-3} , W^{B-4} , or W^{B-5} are simultaneously N;

R_1 is a 5-membered heteroaromatic mono-cyclic moiety containing within the ring 1-3 heteroatoms independently selected from the group consisting of =N-, -N(R_{1-N})-, -O-, and -S-, and having 0-2 substituent selected from R_{1-1} , and further having 0-4 substituents independently selected from F, Cl, Br, or I;

or R_1 is a 9-membered fused-ring moiety having a 6-membered ring fused to a 5-membered ring including the formula

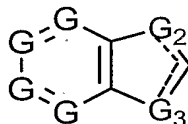


wherein G_1 is O, S or NR_{1-N} ,



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wherein each G is independently CH, $C(R_{1-C})$, or N, and each G_2 and G_3 are independently selected from CH_2 , CH, $C(R_{1-C})$, O, S, N, and $N(R_{1-N})$, provided that both G_2 and G_3 are not simultaneously O, simultaneously S, or simultaneously O and S, or



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wherein each G is independently CH, $C(R_{1-C})$, or N, and each G_2 and G_3 are independently selected from CH_2 , CH, $C(R_{1-C})$, O, S, N, and $N(R_{1-N})$, provided that each 9-membered fused-ring moiety has 0-1 substituent selected from R_{1-1} , and further having 0-3 substituents independently selected from F, Cl, Br, or I, wherein the R_1 moiety attaches to other substituents as defined in formula I at any position as valency allows;

15

Each R_{1-C} is independently a bond, R_{1-1} , F, Cl, Br, or I, provided that there is only one bond and further provided that R_1 can have only up to one substituent from R_{1-1} , and up to 3 substituents from halogen;

20

R_{1-N} is H, alkyl, haloalkyl, substituted alkyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, or substituted heterocycloalkyl;

R_{1-1} is alkyl, substituted alkyl, haloalkyl, $-OR_{1-2}$, $-SR_{1-2}$, $-CN$, $-NO_2$, $-N(R_{1-3})_2$;

25

Each R_{1-2} is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

Each R_{1-3} is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

R_2 is a 6-membered heteroaromatic mono-cyclic moiety containing within the ring 1-4 heteroatoms selected from =N- and having 0-1 substituent selected from R_{2-1} and 0-3 substituent(s) independently selected from F, Cl, Br, or I;

or R_2 is 10-membered heteroaromatic bi-cyclic moieties containing within one or both rings 1-3 heteroatoms selected from =N-, each 10-membered fused-ring moiety having 0-1 substituent selected from R_{2-1} and 0-3 substituent(s) independently selected from F, Cl, Br, or I, wherein the R_2 moiety attaches to other substituents as defined in formula I at any position as valency allows;

R_{2-1} is alkyl, substituted alkyl, haloalkyl, $-OR_{2-2}$, $-SR_{2-2}$, $-CN$, $-NO_2$, $-N(R_{2-3})_2$;

Each R_{2-2} is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

Each R_{2-3} is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

R_7 is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

R_8 is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

Each R_9 is independently H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

R_{10} is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

or pharmaceutical composition, pharmaceutically acceptable salt, racemic mixture, or pure enantiomer thereof useful to treat any one of or combination of cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), senile dementia, schizophrenia or psychosis and related associated cognitive deficits, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, depression, general anxiety disorder, age-related macular degeneration, Parkinson's disease, tardive dyskinesia, Pick's disease, post traumatic stress disorder, dysregulation of food intake including bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, glaucoma, neurodegeneration associated with glaucoma, symptoms associated with pain; pain and inflammation (rheumatoid arthritis; rheumatoid spondylitis; muscle degeneration; osteoporosis; osteoarthritis; psoriasis; contact dermatitis; bone resorption diseases; atherosclerosis; Paget's disease; uveitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); Crohn's disease; rhinitis; ulcerative colitis; anaphylaxis; asthma; Reiter's syndrome; tissue rejection of a graft; ischemia reperfusion injury; brain trauma; stroke; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever and myalgias due to infection; HIV-1, HIV-2, and HIV-3; cytomegalovirus (CMV); influenza; adenovirus; a herpes virus (including HSV-1, HSV-2); or herpes zoster); cancer (multiple myeloma; acute and chronic myelogenous leukemia; or cancer-associated cachexia); diabetes (pancreatic beta cell destruction; or type I and type II diabetes); wound healing (healing burns, and wounds in general including from surgery); bone fracture healing; ischemic heart disease, or stable angina pectoris.

30

Embodiments of the invention may include one or more or combination of the following.

The compounds of Formula I are used to treat, or are used to make a medicament to treat, a mammal where the mammal receives symptomatic relief from activation of an alpha 7 nAChR; these diseases or conditions, include, but are not limited to, any one or more or combination of the following: cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), senile dementia, schizophrenia or psychosis and related associated cognitive deficits, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, depression, general anxiety disorder, age-related macular degeneration, Parkinson's disease, tardive dyskinesia, Pick's disease, post traumatic stress disorder, dysregulation of food intake including bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, glaucoma, neurodegeneration associated with glaucoma, or symptoms associated with pain. The compounds of Formula I are also useful to treat or useful to prepare a medicament to treat diseases or conditions where a mammal would receive symptomatic relief from the administration of a compound of Formula I to decrease levels of TNF- α ; these diseases or conditions, including, but are not limited to, any one or more or combination of the following: inflammation; pain; cancer; or diabetes. Types of inflammation and/or pain that are to be treated include, but are not limited to, any one or more of the following: rheumatoid arthritis; rheumatoid spondylitis; muscle degeneration; osteoporosis; osteoarthritis; psoriasis; contact dermatitis; bone resorption diseases; atherosclerosis; Paget's disease; uveitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); Crohn's disease; rhinitis; ulcerative colitis; anaphylaxis; asthma; Reiter's syndrome; tissue rejection of a graft; ischemia reperfusion injury; brain trauma; stroke; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever and myalgias due to infection; HIV-1, HIV-2, and HIV-3; cytomegalovirus (CMV); influenza; adenovirus; a herpes virus (including HSV-1, HSV-2); or herpes zoster. Types of cancer that are to be treated include, but are not limited to, any one or more

of the following: multiple myeloma; acute and chronic myelogenous leukemia; or cancer-associated cachexia. The compounds of the present invention can be used to treat, or be used to prepare a medicament to treat, the TNF- α aspects associated with pancreatic beta cell destruction; or type I and type II diabetes. The compounds of the present invention are also useful to treat, or to prepare a medicament to be used to treat, diseases or conditions where a mammal would receive symptomatic relief from the increase in vascular angiogenesis; these disease include, but are not limited to, any one or more of the following: wound healing (healing burns, and wounds in general including from surgery), bone fracture healing, ischemic heart disease, and stable angina pectoris.

In another aspect, the invention includes treating, or making medicament(s) to treat, a mammal suffering from schizophrenia or psychosis and cognitive deficits associated with them by administering compounds of Formula I in conjunction with antipsychotic drugs (also called anti-psychotic agents), and optionally also with an agonist of the alpha 7 nAChR, especially when levels of an endogenous agonist are suboptimal. There can be one or more than one medicament. One medicament can comprise the compound of formula I, an antipsychotic agent, and/or an alpha 7 nAChR agonist, or there can be a separate medicament for each separately or any combination, e.g., one medicament could have the compound of Formula I and an alpha 7 nAChR agonist and the other medicament could have the antipsychotic agent.

The compounds of the present invention can also be administered in combination with other agents when treating symptoms associated with infection, inflammation, cancer, or diabetes. For treating these diseases or conditions, a medicament can be prepared comprising a compound of formula I. The same medicament or separate medicament(s), can be used comprising any one of the following: an antibacterial; antiviral agent; an anticancer agent and/or antiemetic agent; or at least one agent to treat diabetes. For example, the compound of Formula I can be co-administered with an antibacterial or antiviral agent, as one medicament or as two separate medicament, to treat an infection, for example, but not limiting, rhinitis. The compound of Formula I can also be co-administered with an anticancer agent and/or antiemetic agent when the disease or condition being treated is cancer, so there could be one medicament or separate medicaments for each agent. And, the

compound of Formula I can be co-administered with agents to treat diabetes in one medicament or as separate medicaments.

In a combination therapy, the compounds of Formula I and the other agent(s) can be administered simultaneously or at separate intervals. When administered simultaneously, the compounds of Formula I and the other agent(s) can be incorporated into a single pharmaceutical composition, e.g., a pharmaceutical combination therapy composition. Alternatively, more than one, e.g., two, separate compositions, i.e., one containing a compound of Formula I and the other containing, for example, the psychostimulant, can be administered.

A pharmaceutical combination therapy composition can also be used to treat ADHD, using, for example, but not for limitation, psychostimulants and/or monoamine reuptake inhibitors. This composition can also optionally include an $\alpha 7$ nAChR agonist. While psychostimulants and monoamine reuptake inhibitors control the activity level, and attention, they are not effective in treating the co-morbid or concomitant deficit in cognition that is associated with ADHD. The combination therapy will be more effective at treating this disease because the ability of the mammal to regulate an $\alpha 7$ nAChR agonist will treat the underlying cognitive dysfunction in the disorder and the other two classes of drugs will treat the behavioral problems associated with ADHD. Psychostimulants used for these compositions include, but are not limited to: methylphenidate (Ritalin) administered at about 0.01 to about 0.85 mg/kg/day; dextroamphetamine (Dexedrine) administered at about 0.07 to about 0.85 mg/kg/day; amphetamine (Adderall) administered at about 0.05 to about 0.6 mg/kg/day; and pemoline (Cylert) administered at about 0.1 to about 1.6 mg/kg/day. Monoamine Reuptake inhibitors for these compositions include, but are not limited to: desipramine (Norpramin) administered at about 0.5 to about 5.0 mg/kg/day; nortriptyline administered at about 0.1 to about 3.0 mg/kg/day; atomoxetine (Strattera) administered at about 0.1 to about 3.0 mg/kg/day; reboxetine administered at about 0.03 to about 3.0 mg/kg/day; fluoxetine (Prozac) administered at about 0.2 to about 20 mg/kg/day; tomoxetine administered at about at about 0.1 to about 1.1 mg/kg/day; bupropion (Wellbutrin) administered at about at about 1.0 to about 1.1 mg/kg/day; or modafonil (Provigil) administered at about at about 1.0 to about 5.7 mg/kg/day. The medicament(s) used to treat ADHD can comprise any combination or single item of the following: a compound of formula I, a

psychostimulant, a monoamine reuptake inhibitor and/or an $\alpha 7$ nAChR agonist, or separate medicament(s) can be prepared comprising a any combination of them.

There are also three forms of combination therapies to enhance the activity of a positive allosteric modulator in the presence of an agonist of the $\alpha 7$ nAChR. The first combination therapy is to use a positive allosteric modulator of the $\alpha 7$ nAChR with drugs such as Aricept and Reminyl that inhibit the activity of acetylcholinesterase. Acetylcholinesterase is the enzyme that is primarily responsible for degrading ACh. Drugs such as Aricept and Reminyl which are used to treat Alzheimer's disease, increase ACh levels. The increase in ACh levels leads to an increase in the activity of $\alpha 7$ nAChR and other nicotinic and muscarinic receptors. Thus treating with both acetylcholinesterase inhibitors and a positive allosteric modulator of $\alpha 7$ nAChR will selectively enhance the activity of the $\alpha 7$ nAChR which could provide significant therapeutic benefit for the patient.

The second combination therapy is to use a positive allosteric modulator of the $\alpha 7$ nAChR with a drug that directly activates the $\alpha 7$ nAChR. Drugs that act as receptor agonists and directly activate the $\alpha 7$ nAChR have therapeutic potential but they also carry the liability that prolonged exposure may lead to a loss of efficacy. Using a direct acting agonist of the $\alpha 7$ nAChR in combination with a positive allosteric modulator of the $\alpha 7$ nAChR make both classes of drugs more effective.

The third combination therapy is to use a positive allosteric modulator of $\alpha 7$ nAChR in combination with nutritional supplements including phosphatidylserine, phosphatidylcholine, or choline that act by increasing levels of ACh in the brain. As previously mentioned, an increase in ACh leads to an increase in the activity of $\alpha 7$ nAChR and other nicotinic and muscarinic receptors. Thus, treating with cholinergic nutritional supplements and a positive allosteric modulator of $\alpha 7$ nAChR will selectively enhance the activity of the $\alpha 7$ nAChR to provide significant therapeutic benefit for the patient.

A pharmaceutical combination therapy composition can include therapeutically effective amounts of the compounds of Formula I, and a therapeutically effective amount of the other drug(s)/agent(s). These compositions may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or

administered by intramuscular intravenous routes. The compounds can be administered rectally, topically, orally, or sublingually.

In a combination therapy, the compounds of Formula I and the other drug(s) can be administered simultaneously or at separate intervals. When administered simultaneously the compounds of Formula I and the other drug(s) can be incorporated into a single pharmaceutical composition, e.g., a pharmaceutical combination therapy composition. Alternatively, two or more separate compositions, i.e., one containing compounds of Formula I and the other containing the other drug(s), can be administered simultaneously.

When separately administered, therapeutically effective amounts of compositions containing compounds of Formula I and the other drug(s) are administered on a different schedule. One may be administered before the other as long as the time between the two administrations falls within a therapeutically effective interval. A therapeutically effective interval is a period of time beginning when one of either (a) the compounds of Formula I, or (b) the other drug(s) is administered to a human and ending at the limit of the beneficial effect in the treatment of the disease or condition using the combination of (a) and (b). The methods of administration of the compounds of Formula I and the other drug(s) may vary. Thus, either agent or both agents may be administered rectally, topically, orally, sublingually, or parenterally.

The amount of therapeutically effective compound of Formula I that is administered and the dosage regimen for treating a disease or condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound(s) employed, and thus may vary widely. The compositions contain well known carriers and excipients in addition to a therapeutically effective amount of compounds of Formula I. The pharmaceutical compositions may contain the compound of Formula I in the range of about 0.001 to 100 mg/kg/day for an adult, preferably in the range of about 0.01 to about 50 mg/kg/day for an adult. A total daily dose of about 1 to 1000 mg of a compound of Formula I may be appropriate for an adult. The daily dose can be administered in one to four doses per day. These compositions may be formulated with common excipients, diluents or carriers, and compressed into tablets, or

formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds of Formula I can be administered rectally, topically, orally, sublingually, or parenterally and maybe formulated as sustained relief dosage forms and the like.

- 5 The combined administration of the compounds of Formula I and the other agent(s) is expected to require less of the generally-prescribed dose for either agent when used alone and or is expected to result in less frequent administration of either or both agents. The skilled clinician may in fact learn that behavioral problems are secondary to the cognitive problems and can be treated with lower dosages of the
- 10 other agent(s). Determining such dosages and routes of administration should be a routine determination by one skilled in the art of treating patients with the diseases or conditions discussed herein.

A group of compounds of Formula I within the scope of the invention includes compounds where X is O or S.

- 15 Another group of compounds of Formula I includes compounds where each R_A is independently R_{A-1} or R_{A-2} , provided that one R_A is R_{A-2} .

Another group of compounds of Formula I includes compounds where each R_{A-1} is independently any one of the following: H, halogen, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, aryl, $-N_3$, $-SCN$, $-CN$, $-NO_2$, $-OR_7$, $-SR_8$, $-S(O)R_8$, $-S(O)_2R_8$, $-N(R_9)_2$, $-C(O)R_{10}$, $-C(O)OR_7$, $-C(O)N(R_9)_2$, $-NR_9C(O)R_{10}$, $-C(R_{10})=NOR_7$, $-S(O)_2N(R_9)_2$, $-NR_9S(O)_2R_8$, $-N(R_9)C(O)N(R_9)_2$.

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- 25 Another group of compounds of Formula I includes compounds where R_{A-2} is any one of the following: R_1 , R_2 , OR_1 , OR_2 , $N(R_{A-3})R_1$, $N(R_{A-3})R_2$, SR_1 , and SR_2 .

Another group of compounds of Formula I includes compounds where X is O; A is phenyl substituted at the 2 and 4 position as allowed by Formula I and optionally substituted at the 5 position as allowed by Formula I; and B is independently any one

30 of thienyl, thiazolyl, furanyl, isothiazolyl, thiadiazolyl, isoxazolyl, oxazolyl, and pyrdinyl, any of which is optionally substituted as allowed by Formula I, for example with alkyl, haloalkyl, or cyano. More specific examples of A include where W^{A-1} and W^{A-4} are CH; W^{A-2} is CH or CR_{A-1} ; W^{A-3} is CR_{A-1} ; and W^{A-5} is CR_{A-2} . More specific

examples of R_{A-1} include halo or OR_7 , where R_7 is alkyl, and substituted alkyl. More specific examples of R_{A-2} include R_1 , OR_1 , NHR_1 , R_2 , OR_2 , and NHR_2 , where R_1 is independently any one of thienyl, thiazolyl, furanyl, isothiazolyl, thiadiazolyl, isoxazolyl, and oxazolyl, and where R_2 is pyridinyl, any of which is optionally substituted as allowed by formula I.

Another group of compounds of Formula I includes compounds where each of R_7 , R_8 , R_9 , and R_{10} are each independently any one of the following: H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl.

Another group of compounds of Formula I includes compounds where R_5 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, haloalkyl, haloalkenyl, haloalkynyl, halocycloalkyl, haloheterocycloalkyl, $-CN$, $-NO_2$, $-OR_3$, $-SR_3$, $-N(R_3)_2$, $-C(O)R_3$, $-C(O)N(R_3)_2$, $-NR_3C(O)R_3$, $-S(O)_2N(R_3)_2$, $-NR_3S(O)_2R_3$, alkyl substituted with 1-4 substituent(s) independently selected from F, Cl, Br, I, or R_6 , cycloalkyl substituted with 1-4 substituent(s) independently selected from F, Cl, Br, I, or R_6 , or heterocycloalkyl substituted with 1-4 substituent(s) independently selected from F, Cl, Br, I, or R_6 .

Another group of compounds of Formula I includes compounds where each R_3 is independently any one of the following: H, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, haloheterocycloalkyl, or phenyl optionally substituted with 0-3 halogens and 0-1 substituent selected from alkyl, $-CF_3$, $-CN$, $-NH_2$, $-NO_2$, and $-OH$.

Another group of compounds of Formula I includes compounds where R_4 is any one of the following: H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, or aryl.

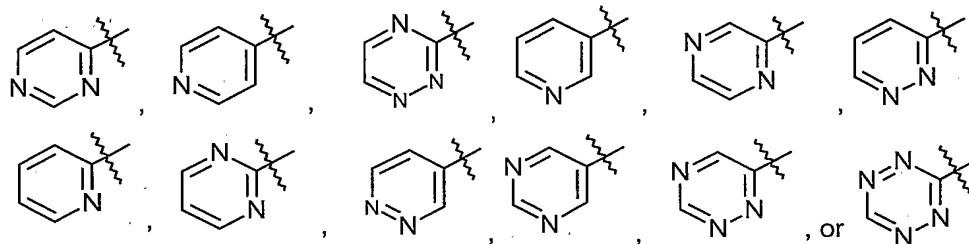
One of ordinary skill in the art will recognize that where alkyl, haloalkyl and substituted alkyl, alkenyl, haloalkenyl and substituted alkenyl, and the like, are allowed, so is lower alkyl, lower haloalkyl, lower substituted alkyl, lower alkenyl, lower haloalkenyl and lower substituted alkenyl, respectively, are also allowed.

Another group of compounds of Formula I includes compounds where R_6 is any one of the following: $-CF_3$, $-CN$, $-NO_2$, $-OR_3$, $-SR_3$, $-N(R_3)_2$, $-C(O)R_3$,

$-C(O)N(R_3)_2$, $-NR_3C(O)R_3$, $-S(O)_2N(R_3)_2$, or $-NR_3S(O)_2R_3$.

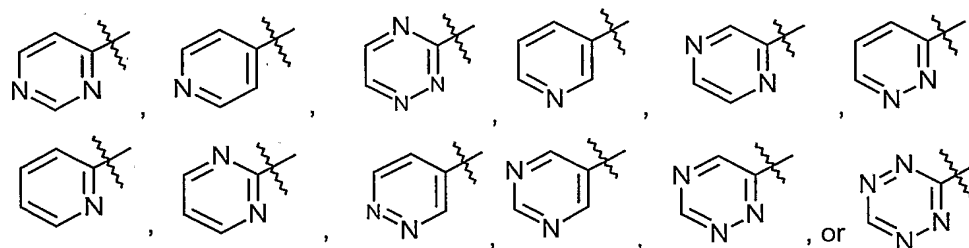
Non-inclusive examples of R_1 and R_2 include, but are not limited to, any one of the following: thienyl, benzothienyl, pyridyl, thiazolyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, thiadiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl, pyrazolyl, triazolyl, isoxazolyl, oxazolyl, pyrrolyl, isoquinolyl, cinnolyl, indazolyl, indolizyl, phthalazyl, pyridazyl, triazyl, isoindolyl, purinyl, oxadiazolyl, furazyl, benzofurazyl, benzothiophenyl, benzothiazolyl, quinazolyl, quinoxalyl, naphthridyl, and furopyridyl, any of which is optionally substituted as allowed by formula I. One of ordinary skill in the art will recognize the moieties from R_1 and R_2 with how they are defined herein. R_1 and R_2 are referred to as heteroaryls for ease of reference.

Another group of compounds of Formula I includes compounds where A includes, but is not limited to, compounds wherein up to four of W^{A-1} , W^{A-2} , W^{A-3} , W^{A-4} , and W^{A-5} can be N to include the following moieties:



optionally substituted as valency allows and as R_A is defined herein.

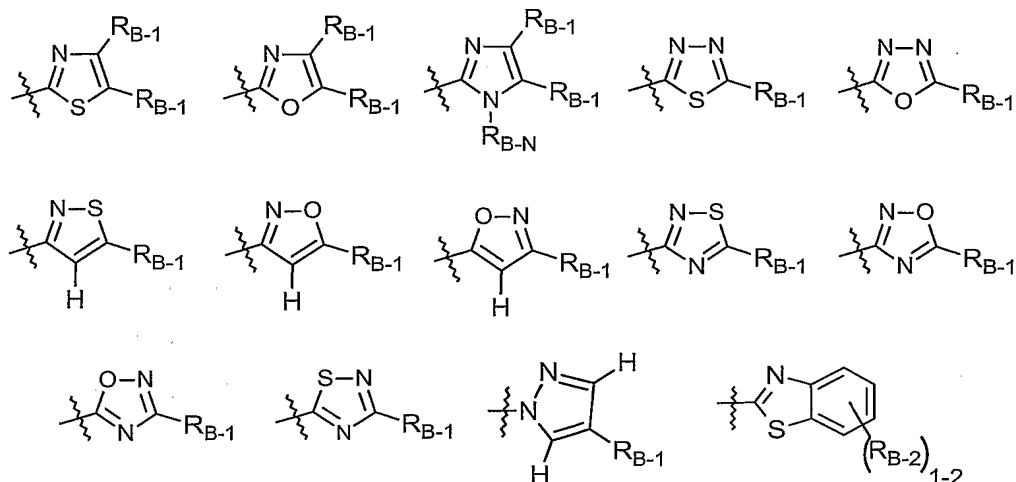
Another group of compounds of Formula I includes compounds where B includes, but is not limited to, compounds wherein W^{B-1} , W^{B-2} , W^{B-3} , W^{B-4} , and W^{B-5} can be N or CR_{B-1} to include the following moieties:



optionally substituted as valency and the definition of Formula I allow and with any definition of R_{B-1} as discussed herein.

Another group of compounds of Formula I includes compounds wherein B includes, but is not limited to, the following moieties that one of ordinary skill in the

art can recognize as fitting within the scope of the structures drawn for B:



- 5 where each R_{B-1} and R_{B-2} have any definition discussed herein and can occur at any carbon where valency allows, and where R_{B-N} has any definition discussed herein and can occur at any nitrogen where valency allows.

The present invention includes, but is not limited to, the following compounds as the free base or a pharmaceutically acceptable salt thereof:

- 10 N-[4-ethoxy-2-(pyridin-4-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 N-[4-ethoxy-2-(pyridin-3-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 N-[4-ethoxy-2-(pyridin-3-ylamino)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[4-ethoxy-2-(pyridin-2-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 15 N-[4-methoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 N-[4-methoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[4-methoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 N-[4-methoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 20 N-[2-(2-furyl)-4-methoxyphenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[2-(2-furyl)-4-methoxyphenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
 N-[4-ethoxy-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[4-ethoxy-2-(2-furyl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 25 N-(4-methoxy-2-thien-2-ylphenyl)-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[2,4-dimethoxy-5-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;

- N-[4-ethoxy-2-(2-furyl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
 N-[4-methoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
 N-[4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
 N-[4-ethoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
 5 N-[4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[4-ethoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-(6-cyanopyridin-3-yl)-N'-[4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]urea;
 10 N-[2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
 N-[2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[4-ethoxy-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea; and
 N-[4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea.

The present invention includes, but is not limited to, the following compounds
 15 as the free base or a pharmaceutically acceptable salt thereof:

- N-[4-ethoxy-5-fluoro-2-(pyridin-4-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 N-[4-ethoxy-5-fluoro-2-(pyridin-3-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 N-[4-ethoxy-5-fluoro-2-(pyridin-3-ylamino)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 20 N-[4-ethoxy-5-fluoro-2-(pyridin-2-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 N-[4-methoxy-5-fluoro-2-(1,3-thiazol-2-yl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 N-[4-methoxy-5-fluoro-2-(1,3-thiazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[4-methoxy-5-fluoro-2-(1,3-oxazol-2-yl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
 25 N-[4-methoxy-5-fluoro-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[5-fluoro-2-(2-furyl)-4-methoxyphenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[5-fluoro-2-(2-furyl)-4-methoxyphenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
 30 N-[4-ethoxy-5-fluoro-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
 N-[4-ethoxy-5-fluoro-2-(2-furyl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;

- N-(5-fluoro-4-methoxy-2-thien-2-ylphenyl)-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[4-ethoxy-5-fluoro-2-(2-furyl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- N-[4-methoxy-5-fluoro-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- 5 N-[4-ethoxy-5-fluoro-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- N-[4-ethoxy-5-fluoro-2-(1,3-thiazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- 10 N-[4-ethoxy-5-fluoro-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[4-ethoxy-5-fluoro-2-(1,3-thiazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-(6-cyanopyridin-3-yl)-N'-[4-ethoxy-5-fluoro-2-(1,3-oxazol-2-yl)phenyl]urea;
- 15 N-[5-fluoro-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- N-[5-fluoro-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[4-ethoxy-5-fluoro-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea;
- and N-[4-ethoxy-5-fluoro-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea;
- 20 N-[5-chloro-4-ethoxy-2-(pyridin-4-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- N-[5-chloro-4-ethoxy-2-(pyridin-3-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- N-[5-chloro-4-ethoxy-2-(pyridin-3-ylamino)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[5-chloro-4-ethoxy-2-(pyridin-2-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- 25 N-[5-chloro-4-methoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- N-[5-chloro-4-methoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[5-chloro-4-methoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- N-[5-chloro-4-methoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- 30 thiadiazol-2-yl]urea;
- N-[5-chloro-2-(2-furyl)-4-methoxyphenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[5-chloro-2-(2-furyl)-4-methoxyphenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;

- N-[5-chloro-4-ethoxy-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[5-chloro-4-ethoxy-2-(2-furyl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- N-(5-chloro-4-methoxy-2-thien-2-ylphenyl)-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- 5 N-[5-chloro-4-ethoxy-2-(2-furyl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- N-[5-chloro-4-methoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- N-[5-chloro-4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- 10 N-[5-chloro-4-ethoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- N-[5-chloro-4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- 15 N-[5-chloro-4-ethoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-(6-cyanopyridin-3-yl)-N'-[5-chloro-4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]urea;
- N-[5-chloro-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- N-[5-chloro-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- 20 N-[5-chloro-4-ethoxy-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea;
- N-[5-chloro-4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea;
- N-[4-(2-methoxy-ethoxy)-2-(pyridin-4-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- 25 N-[4-(2-methoxy-ethoxy)-2-(pyridin-3-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- N-[4-(2-methoxy-ethoxy)-2-(pyridin-3-ylamino)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[4-(2-methoxy-ethoxy)-2-(pyridin-2-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- 30 N-[4-(2-methoxy-ethoxy)-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[4-(2-methoxy-ethoxy)-2-(2-furyl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;

- N-[4-(2-methoxy-ethoxy)-2-(2-furyl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- N-[4-(2-methoxy-ethoxy)-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- 5 N-[4-(2-methoxy-ethoxy)-2-(1,3-thiazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- N-[4-(2-methoxy-ethoxy)-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[4-(2-methoxy-ethoxy)-2-(1,3-thiazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- 10 N-(6-cyanopyridin-3-yl)-N'-[4-(2-methoxy-ethoxy)-2-(1,3-oxazol-2-yl)phenyl]urea;
- N-[4-(2-methoxy-ethoxy)-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea;
- N-[4-(2-methoxy-ethoxy)-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea;
- 15 N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(pyridin-4-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(pyridin-3-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- 20 N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(pyridin-3-ylamino)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(pyridin-2-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;
- 25 N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(2-furyl)phenyl]-N'-(5-methylisoxazol-3-yl)urea;
- N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(2-furyl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;
- 30 N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(1,3-thiazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea;

N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;

N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(1,3-thiazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea;

5 N-(6-cyanopyridin-3-yl)-N'-[5-fluoro-4-(2-methoxy-ethoxy)-2-(1,3-oxazol-2-yl)phenyl]urea;

N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea; and

10 N-[5-fluoro-4-(2-methoxy-ethoxy)-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea.

The present invention also includes isotopically labeled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be
15 incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine iodine, and chlorine, such as ^2H , ^3H , ^{13}C , ^{11}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{123}I , and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the
20 aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and
25 detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

Isotopically labeled compounds of Formula I can generally be prepared by
30 carrying out the synthetic procedures described herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. Isotopically labeled reagents are described, for example, by Langstrom in *Acta Chem. Scand.* S37: 147 (1990). Introducing ^{11}C -labeled agonists of nAChR has been described in Dolle, Frederic, et

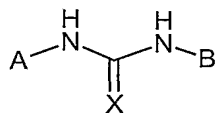
al, *J. Labelled Cps Radiopharm.*, 2001; **44**: 785-795. For a general discussion of nuclear imaging, see, "Nuclear Imaging in Drug Discovery, Development, and Approval, H.D. Burns, et al. (Eds).

The present invention also includes compounds for use in photoaffinity labeling experiments. One technique for the biochemical characterization of receptors is photoaffinity labeling using a photolabile molecule, or probe, which binds with high affinity to a receptor and can be irreversibly incorporated into the receptor under the influence of ultraviolet light. In order to have an effective and useful photoaffinity probe, several requirements must be met. First, the probe must have good biological activity at the same target protein relative to the parent compounds of interest. Second, it must have a reactive group which can covalently bond to the target site upon photoactivation. For example, the azido group is chemically inert until photoactivated by UV light. Upon photolysis it generates a highly reactive nitrene which inserts into either the peptide backbone or the amino acid side chains of the protein to which it is bound. This insertion forms a covalent linkage between the photoprobe and the protein allowing it to be permanently tagged for identification.

Further aspects and embodiments of the invention may become apparent to those skilled in the art from a review of the following detailed description, taken in conjunction with the examples and the appended claims. While the invention is susceptible of embodiments in various forms, described hereafter are specific embodiments of the invention with the understanding that the present disclosure is intended as illustrative, and is not intended to limit the invention to the specific embodiments described herein.

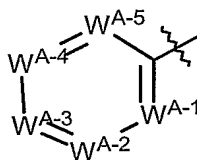
DETAILED DESCRIPTION OF INVENTION

Surprisingly, we have found that compounds of Formula I:



wherein X is O or S;

A is



wherein each W^{A-1} , W^{A-2} , W^{A-3} , W^{A-4} , and W^{A-5} are independently N or CR_A , provided that no more than four of W^{A-1} , W^{A-2} , W^{A-3} , W^{A-4} , or W^{A-5} are simultaneously N;

5 Each R_A is R_{A-1} or R_{A-2} , provided that one R_A is R_{A-2} ;

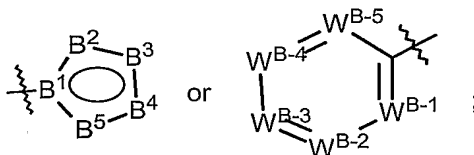
Each R_{A-1} is independently H, halogen, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, aryl, $-N_3$, $-SCN$, $-CN$, $-NO_2$, $-OR_7$, $-SR_8$,
 10 $-S(O)R_8$, $-S(O)_2R_8$, $-N(R_9)_2$, $-C(O)R_{10}$, $-C(O)OR_7$, $-C(O)N(R_9)_2$, $-NR_9C(O)R_{10}$, $-C(R_{10})=NOR_7$, $-S(O)_2N(R_9)_2$, $-NR_9S(O)_2R_8$, $-N(R_9)C(O)N(R_9)_2$;

R_{A-2} is R_1 , R_2 , OR_1 , OR_2 , $N(R_{A-3})R_1$, $N(R_{A-3})R_2$, SR_1 , and SR_2 ;

R_{A-3} is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl,
 15 substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

B is a five or six-membered aromatic ring having up to 4 heteroatoms selected from $-O-$, $-N(R_{B-3})-$, $=N-$, or $-S-$;

20 wherein B is



B^1 is N, or C;

B^2 , B^3 , B^4 , and B^5 are independently N, O, S, C, provided that when valency allows, the N can have a third bond to R_{B-3} , and further provided that when valency
 25 allows, the C can have a fourth bond to R_{B-1} ;

Each R_{B-1} is independently H, halogen, alkyl, haloalkyl, substituted alkyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, heterocycloalkyl,

haloheterocycloalkyl, substituted heterocycloalkyl, aryl, -CN, -N₃, -NO₂, -COR₁₀, -CO₂R₇, -CON(R₉)₂, -C(R₁₀)=NOR₇, -SCN, -OR₇, -N(R₉)₂, -SR₈, -SOR₈, -SO₂R₈, -SN(R₉)₂, -SON(R₉)₂, -SO₂N(R₉)₂; or

when two R_{B-1} are on adjacent carbon atoms, the two R_{B-1} may combine to form a 5-7-membered ring fused to the 5 or 6 membered ring giving a fused-bicyclic-ring system; wherein the 5-7-membered ring is saturated or unsaturated having up to two heteroatoms selected from -O-, -S-, -N(R_{B-3})-, or -N= and further having substitution where valency allows on the 5-7-membered ring with up to 2 substituents independently selected from R_{B-2};

Each R_{B-2} is independently H, F, Cl, Br, I, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, haloalkyl, haloalkenyl, haloalkynyl, halocycloalkyl, haloheterocycloalkyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, -CN, -NO₂, -OR₇, -SR₈, -S(O)₂R₈, -S(O)R₈, -OS(O)₂R₈, -N(R₉)₂, -C(O)R₁₀, -C(S)R₁₀, -C(O)₂R₇, -C(O)N(R₉)₂, -NR₉C(O)R₁₀, -S(O)₂N(R₉)₂, -NR₉S(O)₂R₈, -N(R₉)C(O)N(R₉)₂, or aryl;

R_{B-3} is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

Each W^{B-1}, W^{B-2}, W^{B-3}, W^{B-4}, and W^{B-5} are independently N or CR_{B-1}, provided that no more than 4 of W^{B-1}, W^{B-2}, W^{B-3}, W^{B-4}, or W^{B-5} are simultaneously N;

Halogen (used interchangeably with "halo") is F, Br, Cl, or I;

Alkyl is both straight- and branched-chain moieties having from 1-6 carbon atoms;

Lower alkyl is both straight- and branched-chain moieties having from 1-4 carbon atoms;

Haloalkyl is an alkyl moiety having from 1-6 carbon atoms and having 1 to (2n+1) substituent(s) independently selected from F, Cl, Br, or I, where n is the maximum number of carbon atoms in the moiety;

Lower haloalkyl is lower alkyl having 1 to (2n+1) substituent(s) independently selected from F, Cl, Br, or I, where n is the maximum number of carbon atoms in the moiety;

Substituted alkyl is an alkyl moiety from 1-6 carbon atoms and having 0-3 substituents independently selected from F, Cl, Br, or I, and further having 1 substituent selected from -CN, -NO₂, -OR₃, -SR₃, -N(R₃)₂, -C(O)R₃, -C(O)N(R₃)₂, -NR₃C(O)R₃, -S(O)₂N(R₃)₂, -NR₃(O)₂R₃, phenyl, or substituted phenyl;

5 Lower substituted alkyl is lower alkyl having 0-3 substituents independently selected from F, Cl, Br, or I, and further having 1 substituent selected from -CN, -NO₂, -OR₃, -SR₃, -N(R₃)₂, -C(O)R₃, -C(O)N(R₃)₂, -NR₃(O)R₃, -S(O)₂N(R₃)₂, -NR₃(O)₂R₃, phenyl, or substituted phenyl;

Alkenyl is straight- and branched-chain moieties having from 2-6 carbon
10 atoms and having at least one carbon-carbon double bond;

Lower alkenyl is straight- and branched-chain moieties having from 2-4 carbon atoms and having at least one carbon-carbon double bond;

Haloalkenyl is an alkenyl moiety having from 2-6 carbon atoms and having 1
to (2n-1) substituent(s) independently selected from F, Cl, Br, or I where n is the
15 maximum number of carbon atoms in the moiety;

Lower haloalkenyl is lower alkenyl having 1 to (2n-1) substituent(s) independently selected from F, Cl, Br, or I where n is the maximum number of carbon atoms in the moiety;

Substituted alkenyl is an unsaturated alkenyl moiety having from 2-6 carbon
20 atoms and having 0-3 substituents independently selected from F, Cl, Br, or I, and further having 1 substituent selected from -CN, -NO₂, -OR₃, -SR₃, -N(R₃)₂, -C(O)R₃, -C(O)N(R₃)₂, -NR₃C(O)R₃, -S(O)₂N(R₃)₂, -NR₃C(O)₂R₃, phenyl, or substituted phenyl;

Lower substituted alkenyl is lower alkenyl having 0-3 substituents
25 independently selected from F, Cl, Br, or I, and further having 1 substituent selected from -CN, -NO₂, -OR₃, -SR₃, -N(R₃)₂, -C(O)R₃, -C(O)N(R₃)₂, -NR₃C(O)R₃, -S(O)₂N(R₃)₂, -NR₃C(O)₂R₃, phenyl, or substituted phenyl;

Alkynyl is straight- and branched-chained moieties having from 2-6 carbon
atoms and having at least one carbon-carbon triple bond;

30 Haloalkynyl is an alkynyl moiety having from 2-6 carbon atoms and having 1 to (2n-3) substituent(s) independently selected from F, Cl, Br, or I where n is the maximum number of carbon atoms in the moiety;

Substituted alkynyl is an unsaturated alkynyl moiety having from 2-6 carbon atoms and having 0-3 substituents independently selected from F, Cl, Br, or I, and further having 1 substituent selected from -CN, -NO₂, -OR₃, -SR₃, -N(R₃)₂, -C(O)R₃, -C(O)N(R₃)₂, -NR₃C(O)R₃, -S(O)₂N(R₃)₂, -NR₃C(O)₂R₃, phenyl, or substituted phenyl;

Cycloalkyl is a cyclic alkyl moiety having from 3-6 carbon atoms;

Lower cycloalkyl is a cyclic alkyl moiety having from 3-4 carbon atoms;

Halocycloalkyl is a cyclic moiety having from 3-6 carbon atoms and having 1-4 substituents independently selected from F, Cl, Br, or I;

Substituted cycloalkyl is a cycloalkyl moiety from 3-6 carbon atoms and having 0-3 substituents independently selected from F, Cl, Br, or I and further having 1 substituent selected from -CN, -NO₂, -OR₃, -SR₃, -N(R₃)₂, -C(O)R₃, -C(O)N(R₃)₂, -NR₃C(O)R₃, -S(O)₂N(R₃)₂, -NR₃C(O)₂R₃, phenyl, or substituted phenyl;

Heterocycloalkyl is a cyclic moiety having 4-7 atoms with 1-2 atoms within the ring being -S-, -N(R₄)-, or -O-;

Haloheterocycloalkyl is a cyclic moiety having from 4-7 atoms with 1-2 atoms within the ring being -S-, -N(R₄)-, or -O-, and having 1-4 substituents independently selected from F, Br, Cl, or I;

Substituted heterocycloalkyl is a cyclic moiety having from 4-7 atoms with 1-2 atoms within the ring being -S-, -N(R₄)-, or -O- and having 0-3 substituents independently selected from F, Br, Cl, or I, further having up to 2 oxo (=O) on separate carbon atoms with sufficient valency, and further having 1 substituent selected from -CN, -NO₂, -OR₃, -SR₃, -N(R₃)₂, -C(O)R₃, -C(O)N(R₃)₂, -NR₃C(O)R₃, -S(O)₂N(R₃)₂, -NR₃C(O)₂R₃, phenyl, or substituted phenyl;

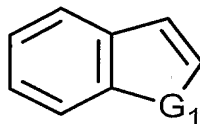
Aryl is phenyl, substituted phenyl, naphthyl, or substituted naphthyl;

Substituted phenyl is a phenyl either having 1-4 substituents independently selected from F, Cl, Br, or I, or having 1 substituent selected from R₅ and 0-3 substituents independently selected from F, Cl, Br, or I;

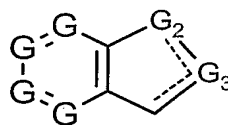
Substituted naphthyl is a naphthalene moiety either having 1-4 substituents independently selected from F, Cl, Br, or I, or having 1 substituent selected from R₅ and 0-3 substituents independently selected from F, Cl, Br, or I, where the substitution can be independently on either only one ring or both rings of said naphthalene moiety;

R_1 is a 5-membered heteroaromatic mono-cyclic moiety containing within the ring 1-3 heteroatoms independently selected from the group consisting of =N-, -N(R_{1-N})-, -O-, and -S-, and having 0-2 substituent selected from R_{1-1} , and further having 0-4 substituents independently selected from F, Cl, Br, or I;

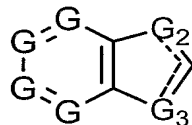
- 5 or R_1 is a 9-membered fused-ring moiety having a 6-membered ring fused to a 5-membered ring including the formula



wherein G_1 is O, S or NR_{1-N} ,



- 10 wherein each G is independently CH, C(R_{1-C}), or N, and each G_2 and G_3 are independently selected from CH_2 , CH, C(R_{1-C}), O, S, N, and N(R_{1-N}), provided that both G_2 and G_3 are not simultaneously O, simultaneously S, or simultaneously O and S, or



- 15 wherein each G is independently CH, C(R_{1-C}), or N, and each G_2 and G_3 are independently selected from CH_2 , CH, C(R_{1-C}), O, S, N, and N(R_{1-N}), provided that each 9-membered fused-ring moiety has 0-1 substituent selected from R_{1-1} , and further having 0-3 substituents independently selected from F, Cl, Br, or I, wherein the R_1 moiety attaches to other substituents as defined in formula I at any position as valency
20 allows;

Each R_{1-C} is independently a bond, R_{1-1} , F, Cl, Br, or I, provided that there is only one bond and further provided that R_1 can have only up to one substituent from R_{1-1} , and up to 3 substituents from halogen;

- R_{1-N} is H, alkyl, haloalkyl, substituted alkyl, cycloalkyl, halocycloalkyl,
25 substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, or substituted heterocycloalkyl;

R_{1-1} is alkyl, substituted alkyl, haloalkyl, -OR₁₋₂, -SR₁₋₂, -CN, -NO₂,

-N(R₁₋₃)₂;

Each R₁₋₂ is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

Each R₁₋₃ is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

R₂ is a 6-membered heteroaromatic mono-cyclic moiety containing within the ring 1-4 heteroatoms selected from =N- and having 0-1 substituent selected from R₂₋₁ and 0-3 substituent(s) independently selected from F, Cl, Br, or I;

or R₂ is 10-membered heteroaromatic bi-cyclic moieties containing within one or both rings 1-3 heteroatoms selected from =N-, each 10-membered fused-ring moiety having 0-1 substituent selected from R₂₋₁ and 0-3 substituent(s) independently selected from F, Cl, Br, or I, wherein the R₂ moiety attaches to other substituents as defined in formula I at any position as valency allows;

R₂₋₁ is alkyl, substituted alkyl, haloalkyl, -OR₂₋₂, -SR₂₋₂, -CN, -NO₂, -N(R₂₋₃)₂;

Each R₂₋₂ is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

Each R₂₋₃ is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

Each R₃ is independently H, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, haloheterocycloalkyl, or phenyl optionally substituted with 0-3 halogens and 0-1 substituent selected from alkyl, -CF₃, -CN, -NH₂, -NO₂, and -OH;

R₄ is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, or aryl;

R₅ is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, haloalkyl, haloalkenyl, haloalkynyl, halocycloalkyl, haloheterocycloalkyl, -CN, -NO₂, -OR₃, -SR₃, -N(R₃)₂, -C(O)R₃, -C(O)N(R₃)₂, -NR₃C(O)R₃, -S(O)₂N(R₃)₂, -NR₃S(O)₂R₃, alkyl substituted with 1-4 substituent(s) independently selected from F, Cl, Br, I, or R₆, cycloalkyl substituted with 1-4 substituent(s) independently selected from F, Cl, Br, I, or R₆, or heterocycloalkyl substituted with 1-4 substituent(s) independently selected from F, Cl, Br, I, or R₆;

R_6 is $-CF_3$, $-CN$, $-NO_2$, $-OR_3$, $-SR_3$, $-N(R_3)_2$, $-C(O)R_3$, $-C(O)N(R_3)_2$, $-NR_3C(O)R_3$, $-S(O)_2N(R_3)_2$, or $-NR_3S(O)_2R_3$;

R_7 is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

R_8 is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

Each R_9 is independently H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

R_{10} is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

or pharmaceutical composition, pharmaceutically acceptable salt, racemic mixture, or pure enantiomer thereof useful to treat any one of or combination of cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), senile dementia, schizophrenia or psychosis and related associated cognitive deficits, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, depression, general anxiety disorder, age-related macular degeneration, Parkinson's disease, tardive dyskinesia, Pick's disease, post traumatic stress disorder, dysregulation of food intake including bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, glaucoma, neurodegeneration associated with glaucoma,

symptoms associated with pain; pain and inflammation (rheumatoid arthritis; rheumatoid spondylitis; muscle degeneration; osteoporosis; osteoarthritis; psoriasis; contact dermatitis; bone resorption diseases; atherosclerosis; Paget's disease; uveitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); Crohn's disease; rhinitis; ulcerative colitis; anaphylaxis; asthma; Reiter's syndrome; tissue rejection of a graft; ischemia reperfusion injury; brain trauma; stroke; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever and myalgias due to infection; HIV-1, HIV-2, and HIV-3; cytomegalovirus (CMV); influenza; adenovirus; a herpes virus (including HSV-1, HSV-2); or herpes zoster); cancer (multiple myeloma; acute and chronic myelogenous leukemia; or cancer-associated cachexia); diabetes (pancreatic beta cell destruction; or type I and type II diabetes); wound healing (healing burns, and wounds in general including from surgery); bone fracture healing; ischemic heart disease, or stable angina pectoris.

15 In another aspect, the invention includes a combination therapy for treating a mammal or preparing a medicament to treat a mammal as discussed herein. The compounds of Formula I and the other drug(s)/agent(s) can be administered simultaneously or at separate intervals. When administered simultaneously the compounds of Formula I and the other drug(s)/agent(s) can be incorporated into a single pharmaceutical composition. Alternatively, separate compositions, i.e., one containing compounds of Formula I and one or more containing the other drug(s), can be administered during a therapeutic interval.

A positive allosteric modulator of $\alpha 7$ nAChR will effectively activate the endogenous $\alpha 7$ nAChR if there is sufficient agonist in the brain to at least partially stimulate this receptor. Therefore, a positive allosteric modulator of $\alpha 7$ nAChR can be administered alone to treat the disease or conditions discussed herein. In certain diseases, however, it is possible that the full therapeutic efficacy of a positive allosteric modulator of $\alpha 7$ nAChR will be limited by suboptimal levels of agonist which in turn leads to a suboptimal activation of the endogenous $\alpha 7$ nAChR in the presence of a positive allosteric modulator. In such cases, the positive allosteric modulator of $\alpha 7$ nAChR is administered in combination with another agent that affects the level of agonist.

The present invention includes the intermediates, the processes to make them and the compounds of the present invention and salts thereof, pharmaceutical compositions containing the active compounds of the present invention, and methods to treat the identified diseases.

5 The compounds of Formula I exist in tautomeric or enantiomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, e.g., fractional crystallization, or chiral HPLC. Alternatively, the individual enantiomers may be made by reaction of the appropriate
10 optically active starting materials under reaction conditions which will not cause racemization.

Abbreviations which are well known to one of ordinary skill in the art may be used (e.g., "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" or "hr" or "hrs" for hour or hours, "min" for minute or minutes, and "rt" for room temperature).

15 All temperatures are in degrees Centigrade.

Room temperature is within the range of 15-25 degrees Celsius.

Pre-senile dementia is also known as mild cognitive impairment.

ACh refers to acetylcholine.

AChR refers to acetylcholine receptor.

20 nAChR refers to nicotinic acetylcholine receptor.

mAChR refers to muscarinic acetylcholine receptor.

PAM refers to positive allosteric modulator.

5HT₃R refers to the serotonin-type 3 receptor.

α -btx refers to α -bungarotoxin.

25 FLIPR refers to a device marketed by Molecular Devices, Inc. designed to precisely measure cellular fluorescence in a high throughput whole-cell assay. (Schroeder et. al., *J. Biomolecular Screening*, 1(2), p 75-80, 1996).

MLA refers to methyllycaconitine.

TLC refers to thin-layer chromatography.

30 HPLC refers to high pressure liquid chromatography.

MeOH refers to methanol.

EtOH refers to ethanol.

IPA refers to isopropyl alcohol.

THF refers to tetrahydrofuran.

DMSO refers to dimethylsulfoxide.

DMF refers to *N,N*-dimethylformamide.

EtOAc refers to ethyl acetate.

5 TMS refers to tetramethylsilane.

TEA refers to triethylamine.

DIEA refers to diisopropylethylamine.

DMAP refers to 4-(dimethylamino)pyridine.

BINAP refers to racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

10 Pd₂(dba) refers to tris(dibenzylideneacetone)dipalladium (0).

Ether refers to diethyl ether.

Na₂SO₄ refers to sodium sulfate.

K₂CO₃ refers to potassium carbonate.

MgSO₄ refers to magnesium sulfate.

15 When Na₂SO₄, K₂CO₃, or MgSO₄ is used as a drying agent, it is anhydrous.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C₁₋₆ alkyl refers to alkyl of
20 one to six carbon atoms.

Mammal denotes human and other mammals.

Brine refers to an aqueous saturated sodium chloride solution.

Equ means molar equivalents.

IR refers to infrared spectroscopy.

25 Lv refers to leaving groups within a molecule, including Cl, OH, or mixed anhydride.

Parr refers to the name of the company who sells the jars used for conducting reactions under pressure.

PSI means pound per square inch.

30 NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from TMS.

MS refers to mass spectrometry expressed as m/e or mass/charge unit. HRMS refers to high resolution mass spectrometry expressed as m/e or mass/charge unit.

[M+H]⁺ refers to an ion composed of the parent plus a proton. [M-H]⁻ refers to an ion composed of the parent minus a proton. [M+Na]⁺ refers to an ion composed of the parent plus a sodium ion. [M+K]⁺ refers to an ion composed of the parent plus a potassium ion. EI refers to electron impact. ESI refers to electrospray ionization. CI
5 refers to chemical ionization. FAB refers to fast atom bombardment.

Non-inclusive examples of heterocycloalkyl include, but are not limited to, tetrahydrofurano, tetrahydropyrano, pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, pyrazolo, 1,1-dioxidothiomorpholino, azetidino, azetidinono, oxindolo, dihydroimidazolo, and pyrrolidinono.

10 Compounds of the present invention may be in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases, and salts prepared from inorganic acids, and organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, ferric, ferrous,
15 lithium, magnesium, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, such as arginine, betaine, caffeine, choline, N, N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine,
20 glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and the like. Salts derived from inorganic acids include salts of hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, phosphorous acid and the like.
25 Salts derived from pharmaceutically acceptable organic non-toxic acids include salts of C₁₋₆ alkyl carboxylic acids, di-carboxylic acids, and tri-carboxylic acids such as acetic acid, propionic acid, fumaric acid, succinic acid, tartaric acid, maleic acid, adipic acid, and citric acid, and aryl and alkyl sulfonic acids such as toluene sulfonic
30 acids and the like.

By the term "effective amount" of a compound as provided herein is meant a nontoxic but sufficient amount of the compound(s) to provide the desired effect. As pointed out below, the exact amount required will vary from subject to subject,

depending on the species, age, and general condition of the subject, the severity of the disease that is being treated, the particular compound(s) used, the mode of administration, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate effective amount may be determined by one of
5 ordinary skill in the art using only routine experimentation.

The amount of therapeutically effective compound(s) that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route
10 and frequency of administration, and the particular compound(s) employed, and thus may vary widely. The compositions contain well know carriers and excipients in addition to a therapeutically effective amount of compounds of Formula I. The pharmaceutical compositions may contain active ingredient in the range of about 0.001 to 100 mg/kg/day for an adult, preferably in the range of about 0.01 to about 50
15 mg/kg/day for an adult. A total daily dose of about 1 to 1000 mg of active ingredient may be appropriate for an adult. The daily dose can be administered in one to four doses per day.

In addition to the compound(s) of Formula I, the composition for therapeutic use may also comprise one or more non-toxic, pharmaceutically acceptable carrier
20 materials or excipients. The term "carrier" material or "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier and/or diluent and/or adjuvant, or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a
25 capsule or tablet suitable for oral administration. Excipients can include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, polymers, lubricants, glidants, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improve appearance of the composition. Acceptable excipients include lactose,
30 sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for

convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropyl-methyl cellulose, or other methods known to those skilled in the art. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. If desired, other active ingredients may be included in the composition.

In addition to the oral dosing, noted above, the compositions of the present invention may be administered by any suitable route, in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compositions may, for example, be administered parenterally, e.g., intravascularly, intraperitoneally, subcutaneously, or intramuscularly. For parenteral administration, saline solution, dextrose solution, or water may be used as a suitable carrier. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, EtOH, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Compounds of the present invention can enhance the efficacy of agonists at nicotinic receptors, and, are, therefore, referred to as "positive allosteric modulators." Cholinergic receptors normally bind the endogenous neurotransmitter ACh. AChRs in the mammalian central nervous system can be divided into mAChR and nAChR subtypes based on the agonist activities of muscarine and nicotine, respectively. The nAChRs are ligand-gated ion channels containing five subunits. Members of the nAChR gene family have been divided into two groups based on their sequences: α and β . Three of the α subunits ($\alpha 7$, $\alpha 8$, and $\alpha 9$) form functional receptors when expressed alone and presumably form homooligomeric receptors.

$\alpha 7$ nAChR is a ligand-gated Ca^{++} channel formed by a homopentamer of $\alpha 7$ subunits. Previous studies have established that in the central nervous system α -btx binds selectively to this homopentameric, $\alpha 7$ nAChR subtype, and that $\alpha 7$ nAChR has a high affinity binding site for both α -btx and MLA. $\alpha 7$ nAChR is expressed at high

levels in the hippocampus, ventral tegmental area and ascending cholinergic projections from nucleus basalis to thalamocortical areas. $\alpha 7$ nAChR agonists increase neurotransmitter release, and increase cognition, arousal, attention, learning and memory.

5 The serotonin type 3 receptor (5HT₃R) is a member of a superfamily of ligand-gated ion channels, which includes the muscle and neuronal nAChR, the glycine receptor, and the γ -aminobutyric acid type A receptor. Like the other members of this receptor superfamily, the 5HT₃R exhibits a sequence homology with $\alpha 7$ nAChR but functionally the two ligand-gated ion channels are very different. For example, $\alpha 7$ nAChR is rapidly desensitized, is highly permeable to calcium and is activated by acetylcholine and nicotine. 5HT₃R is desensitized slowly, is relatively impermeable to calcium and is activated by serotonin. The pharmacology of the $\alpha 7$ nAChR and 5HT₃R channels is very different. For example, Ondansetron, a highly selective 5HT₃R antagonist, has little activity at the $\alpha 7$ nAChR. The converse is also true. For
10 example, GTS-21, a highly selective $\alpha 7$ nAChR agonist, has little activity at the 5HT₃R.
15

 An allosteric transition state model of the nAChR involves at least a resting state (closed), an activated state (open), and a "desensitized" closed channel state (Changeux, J. and Edelstein, S.J., *Curr. Opin. Neurobiol.* 2001 11(3): 369-77; Itier, V. and Bertrand, D., *FEBS Lett* 2001, 504(3): 118-25). Different nAChR ligands can, therefore, differentially stabilize the conformational state to which they preferentially bind. For example, the agonists ACh and (-)-nicotine drive the nAChR to a desensitized state.
20

 Data from human and animal pharmacological studies establish that nicotinic cholinergic neuronal pathways control many important aspects of cognitive function including attention, learning and memory (Levin, E.D., *Psychopharmacology*, 108:417-31, 1992; Levin, E.D. and Simon B.B., *Psychopharmacology*, 138:217-30, 1998). For example, it is well known that nicotine increases cognition and attention in humans. ABT-418, a compound that activates $\alpha 4\beta 2$ and $\alpha 7$ nAChR, improves
25 cognition and attention in clinical trials of Alzheimer's disease and attention-deficit disorders (Potter, A. et. al., *Psychopharmacology (Berl.)*, 142(4):334-42, Mar. 1999; Wilens, T. E. et. al., *Am. J. Psychiatry*, 156(12):1931-7, Dec. 1999). It is also clear
30

that nicotine and selective but weak $\alpha 7$ nAChR agonists increase cognition and attention in rodents and non-human primates.

However, treatment with nicotinic receptor agonists which act at the same site as ACh is problematic because ACh not only activates, but also blocks receptor activity through processes which include desensitization and uncompetitive blockade (open-channel block). Forman & Miller (1988) *Biophysical J.* 54(1):149-158. Furthermore, prolonged activation may up regulate receptor expression and induce a long-lasting inactivation (Olale, F., et al., *J. Pharmacol. Exp. Ther.* 1997, 283(2):675-83; Kuryatov, A. et al., *Eur. J. Pharmacol.* 2000, 393(1-3):11-21; Kawai, H. and Berg, D.K., *J. Neurochem.* 2001, 78(6):1367-78; Buisson, B. and Bertrand, D., *J. Neurosci.* 2001, 21(6):1819-29). Therefore, agonists of nAChRs can be expected to reduce activity as well as enhance it. At nicotinic receptors in general, and, of particular note, at the $\alpha 7$ -nicotinic receptor, desensitization limits the duration that the channel remains in the active state during agonist application.

The present invention provides a means to increase $\alpha 7$ nAChR function in the brain and other organs, tissues and cells of the body by making these receptors more sensitive to activation by an agonist, including, but not limited to, ACh which is the endogenous agonist. Galantamine, an alkaloid originally obtained from bulbs of snowdrops, is a weak cholinesterase inhibitor and is reported to be a positive allosteric modulator of some nicotinic receptors (Santos, M.D., et al, *Mol. Pharmacol.* 2002, 61(5):1222-1234). The advantage of this invention is that a drug that works as a PAM of the $\alpha 7$ nAChR will provide long-lasting therapeutic value and will have a minimal risk of loss of therapeutic efficacy because of receptor desensitization. A PAM will also be a relatively safe drug because it acts to amplify the actions of an endogenous neurotransmitter.

Schizophrenia is a complex multifactorial illness caused by genetic and non-genetic risk factors that produce a constellation of positive and negative symptoms. The positive symptoms include delusions and hallucinations and the negative symptoms include deficits in affect, attention, cognition and information processing. No single biological element has emerged as a dominant pathogenic factor in this disease. Indeed, it is likely that schizophrenia is a syndrome that is produced by the combination of many low penetrance risk factors. Pharmacological studies established that dopamine receptor antagonists are efficacious in treating the overt

psychotic features (positive symptoms) of schizophrenia such as hallucinations and delusions. Clozapine, an “atypical” antipsychotic drug, is novel because it is effective in treating both the positive and some of the negative symptoms of this disease.

Clozapine’s utility as a drug is greatly limited because continued use leads to an
5 increased risk of agranulocytosis and seizure. No other antipsychotic drug is effective in treating the negative symptoms of schizophrenia. This is significant because the restoration of cognitive functioning is the best predictor of a successful clinical and functional outcome of schizophrenic patients (Green, M.F., *Am J Psychiatry*, 153:321-30, 1996). By extension, it is clear that better drugs are needed to treat the cognitive
10 disorders of schizophrenia in order to restore a better state of mental health to patients with this disorder.

One aspect of the cognitive deficit of schizophrenia can be measured by using the auditory event-related potential (P50) test of sensory gating. In this test, electroencephalographic (EEG) recordings of neuronal activity of the hippocampus
15 are used to measure the subject’s response to a series of auditory “clicks” (Adler, L.E. et. al., *Biol. Psychiatry*, 46:8-18, 1999). Normal individuals respond to the first click with greater degree than to the second click. In general, schizophrenics and schizotypal patients respond to both clicks nearly the same (Cullum, C.M. et. al., *Schizophr. Res.*, 10:131-41, 1993). These data reflect a schizophrenic’s inability to
20 “filter” or ignore unimportant information. The sensory gating deficit appears to be one of the key pathological features of this disease (Cadenhead, K.S. et. al., *Am. J. Psychiatry*, 157:55-9, 2000). Multiple studies show that nicotine normalizes the sensory deficit of schizophrenia (Adler, L.E. et. al., *Am. J. Psychiatry*, 150:1856-61, 1993). Pharmacological studies indicate that nicotine’s effect on sensory gating is via
25 the $\alpha 7$ nAChR (Adler, L.E. et. al., *Schizophr. Bull.*, 24:189-202, 1998). Indeed, the biochemical data indicate that schizophrenics have 50% fewer of $\alpha 7$ nAChR receptors in the hippocampus, thus giving a rationale to partial loss of $\alpha 7$ nAChR functionality (Freedman, R. et. al., *Biol. Psychiatry*, 38:22-33, 1995). Interestingly, genetic data indicate that a polymorphism in the promoter region of the $\alpha 7$ nAChR gene is strongly
30 associated with the sensory gating deficit in schizophrenia (Freedman, R. et. al., *Proc. Nat’l Acad. Sci. USA*, 94(2):587-92, 1997; Myles-Worsley, M. et. al., *Am. J. Med. Genet*, 88(5):544-50, 1999). To date, no mutation in the coding region of the $\alpha 7$

nAChR has been identified. Thus, schizophrenics express the same $\alpha 7$ nAChR as non-schizophrenics.

Selective $\alpha 7$ nAChR agonists may be found using a functional assay on FLIPR (see WO 00/73431 A2). FLIPR is designed to read the fluorescent signal from each well of a 96 or 384 well plate as fast as twice a second for up to 30 minutes. This assay may be used to accurately measure the functional pharmacology of $\alpha 7$ nAChR and 5HT₃R. To conduct such an assay, one uses cell lines that expressed functional forms of the $\alpha 7$ nAChR using the $\alpha 7/5$ -HT₃ channel as the drug target and cell lines that expressed functional 5HT₃R. In both cases, the ligand-gated ion channel was expressed in SH-EP1 cells. Both ion channels can produce robust signal in the FLIPR assay.

A positive allosteric modulator of $\alpha 7$ nAChR will effectively activate the endogenous $\alpha 7$ nAChR if there is sufficient agonist in the brain to at least partially stimulate this receptor. Therefore, a positive allosteric modulator of $\alpha 7$ nAChR can be administered alone to treat the disease or conditions discussed herein.

In certain diseases, however, it is possible that the full therapeutic efficacy of a positive allosteric modulator of $\alpha 7$ nAChR will be limited by suboptimal levels of agonist which in turn leads to a suboptimal activation of the endogenous $\alpha 7$ nAChR in the presence of a positive allosteric modulator. For example but not limitation, it is well established that in Alzheimer's disease, there is a loss of ACh from the brains of the patients with this disease and this loss is correlated with disease progression. In this case, the primary role of combination therapy is to treat patients with therapeutic agents that directly activate the endogenous $\alpha 7$ nAChR in combination with a positive allosteric modulator of $\alpha 7$ nAChR to achieve maximal efficacy. Thus, in Alzheimer's disease, it is likely that the full therapeutic efficacy of a positive allosteric modulator of $\alpha 7$ nAChR could be enhanced if combination therapy is used. This combination therapy applies to other diseases or conditions discussed herein where there is a loss of ACh. One of ordinary skill in the art would recognize for which disease or conditions this combination therapy would be useful.

30

The compounds of the present invention are $\alpha 7$ nAChR PAMs and may be used to treat a wide variety of diseases. For example, they may be used in treating schizophrenia, or psychosis.

Schizophrenia is a disease having multiple aspects. Currently available drugs are generally aimed at controlling the positive aspects of schizophrenia, such as delusions. One drug, Clozapine, is aimed at a broader spectrum of symptoms associated with schizophrenia. This drug has many side effects and is thus not
5 suitable for many patients. Thus, there is a need for a drug to treat the cognitive and attention deficits associated with schizophrenia. Similarly, there is a need for a drug to treat the cognitive and attention deficits associated with schizoaffective disorders, or similar symptoms found in the relatives of schizophrenic patients.

Psychosis is a mental disorder characterized by gross impairment in the
10 patient's perception of reality. The patient may suffer from delusions, and hallucinations, and may be incoherent in speech. His behavior may be agitated and is often incomprehensible to those around him. In the past, the term psychosis has been applied to many conditions that do not meet the stricter definition given above. For example, mood disorders were named as psychoses.

15 There are a variety of antipsychotic drugs. The conventional antipsychotic drugs include Chlorpromazine, Fluphenazine, Haloperidol, Loxapine, Mesoridazine, Molindone, Perphenazine, Pimozide, Thioridazine, Thiothixene, and Trifluoperazine. These drugs all have an affinity for the dopamine 2 receptor.

These conventional antipsychotic drugs have several side effects, including
20 sedation, weight gain, tremors, elevated prolactin levels, akathisia (motor restlessness), dystonia and muscle stiffness. These drugs may also cause tardive dyskinesia. Unfortunately, only about 70% of patients with schizophrenia respond to conventional antipsychotic drugs. For these patients, atypical antipsychotic drugs are available.

25 Atypical antipsychotic drugs generally are able to alleviate positive symptoms of psychosis while also improving negative symptoms of the psychosis to a greater degree than conventional antipsychotics. These drugs may improve neurocognitive deficits. Extrapyramidal (motor) side effects are not as likely to occur with the atypical antipsychotic drugs, and thus, these atypical antipsychotic drugs have a lower
30 risk of producing tardive dyskinesia. Finally these atypical antipsychotic drugs cause little or no elevation of prolactin. Unfortunately, these drugs are not free of side effects. Although these drugs each produce different side effects, as a group the side effects include: agranulocytosis; increased risk of seizures, weight gain, somnolence,

dizziness, tachycardia, decreased ejaculatory volume, and mild prolongation of QTc interval.

In a combination therapy to treat multiple symptoms of diseases such as schizophrenia, the compounds of Formula I and the anti-psychotic drugs can be administered simultaneously or at separate intervals. When administered simultaneously the compounds of Formula I and the anti-psychotic drugs can be incorporated into a single pharmaceutical composition, e.g., a pharmaceutical combination therapy composition. Alternatively, two separate compositions, i.e., one containing compounds of Formula I and the other containing anti-psychotic drugs, can be administered simultaneously. Examples of anti-psychotic drugs, in addition to those listed above, include, but are not limited to, Thorazine, Mellaril, Trilafon, Navane, Stelazine, Permitil, Prolixin, Risperdal, Zyprexa, Seroquel, ZELDOX, Acetophenazine, Carphenazine, Chlorprothixene, Droperidol, Loxapine, Mesoridazine, Molindone, Ondansetron, Pimozide, Prochlorperazine, and Promazine.

A pharmaceutical combination therapy composition can include therapeutically effective amounts of the compounds of Formula I, noted above, and a therapeutically effective amount of anti-psychotic drugs. These compositions may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds can be administered rectally, topically, orally, sublingually, or parenterally and maybe formulated as sustained relief dosage forms and the like.

When separately administered, therapeutically effective amounts of compositions containing compounds of Formula I and anti-psychotic drugs are administered on a different schedule. One may be administered before the other as long as the time between the two administrations falls within a therapeutically effective interval. A therapeutically effective interval is a period of time beginning when one of either (a) the compounds of Formula I, or (b) the anti-psychotic drugs is administered to a human and ending at the limit of the beneficial effect in the treatment of schizophrenia or psychosis of the combination of (a) and (b). The methods of administration of the compounds of Formula I and the anti-psychotic drugs may vary. Thus, either agent or both agents may be administered rectally, topically, orally, sublingually, or parenterally.

As discussed, the compounds of the present invention are $\alpha 7$ nAChR PAMs. Therefore, as another aspect of the present invention, the compounds of the present invention may be used to treat a variety of diseases including cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (also known as mild cognitive impairment), and senile dementia.

Alzheimer's disease has many aspects, including cognitive and attention deficits. Currently, these deficits are treated with cholinesterase inhibitors. These inhibitors slow the break down of acetylcholine, and thereby provide a general nonspecific increase in the activity of the cholinergic nervous system. Since the drugs are nonspecific, they have a wide variety of side effects. Thus, there is a need for a drug that stimulates a portion of the cholinergic pathways and thereby provides improvement in the cognitive and attention deficits associated with Alzheimer's disease without the side effects created by nonspecific stimulation of the cholinergic pathways.

Neurodegeneration is a common problem associated with diseases such as Alzheimer's disease. While the current drugs treat some of the symptoms of this disease, they do not control the underlying pathology of the disease. Accordingly, it would be desirable to provide a drug that can slow the progress of Alzheimer's disease.

Pre-senile dementia (mild cognitive impairment) concerns memory impairment rather than attention deficit problems and otherwise unimpaired cognitive functioning. Mild cognitive impairment is distinguished from senile dementia in that mild cognitive impairment involves a more persistent and troublesome problem of memory loss for the age of the patient. There currently is no medication specifically identified for treatment of mild cognitive impairment, due somewhat to the newness of identifying the disease. Therefore, there is a need for a drug to treat the memory problems associated with mild cognitive impairment.

Senile dementia is not a single disease state. However, the conditions classified under this name frequently include cognitive and attention deficits. Generally, these deficits are not treated. Accordingly, there is a need for a drug that

provides improvement in the cognitive and attention deficits associated with senile dementia.

As discussed, the compounds of the present invention are $\alpha 7$ nAChR PAMs. Therefore, other diseases to be treated with compounds of the present invention include treating the cognitive and attention deficits as well as the neurodegeneration associated with attention deficit disorder, attention deficit hyperactivity disorder (ADHD), mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, depression, general anxiety disorder, age-related macular degeneration, Parkinson's disease, tardive dyskinesia, Pick's disease, post traumatic stress disorder, dysregulation of food intake including bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, glaucoma, or symptoms associated with pain.

Attention deficit disorder is generally treated with methylphenidate, an amphetamine-like molecule that has some potential for abuse. Accordingly, it would be desirable to provide a drug that treats attention deficit disorder while having fewer side effects than the currently used drug.

Attention deficit hyperactivity disorder, otherwise known as ADHD, is a neurobehavioral disorder affecting 3-5% of all American children. ADHD concerns cognitive alone or both cognitive and behavioral actions by interfering with a person's ability to stay on a task and to exercise age-appropriate inhibition. Several types of ADHD exist: a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype. Treatment may include medications such as methylphenidate, dextroamphetamine, or pemoline, which act to decrease impulsivity and hyperactivity and to increase attention. No "cure" for ADHD currently exists. Children with the disorder seldom outgrow it; therefore, there is a need for appropriate medicaments.

The compounds of the present invention can also be combined with a psychostimulant or a monoamine reuptake inhibitor and optionally combined with an $\alpha 7$ nAChR agonist, especially when endogenous agonist is suboptimal.

By combination is meant the administration of the two agents within a month or two or less of each other, preferably within a week and more preferably at about the same time or within a day or two or less of each other.

In a combination therapy to treat ADHD, the compounds of Formula I and the psychostimulant or inhibitor can be administered simultaneously or at separate intervals. When administered simultaneously the compounds of Formula I and the psychostimulants or monoamine reuptake inhibitors can be incorporated into a single pharmaceutical composition, e.g., a pharmaceutical combination therapy composition. Alternatively, two separate compositions, i.e., one containing compounds of Formula I and the other containing the psychostimulants or monoamine reuptake inhibitors.

A pharmaceutical combination therapy composition can include therapeutically effective amounts of the compounds of Formula I, noted herein, and a therapeutically effective amount of the psychostimulants or monoamine reuptake inhibitors. While psychostimulants and monoamine reuptake inhibitors control the activity level, and attention, they are not effective in treating the co-morbid or concomitant deficit in cognitive that is associated with ADHD. The combination therapy will be more effective at treating this disease because a PAM and optionally an $\alpha 7$ nAChR agonist will treat the underlying cognitive dysfunction in the disorder and the other two classes of drugs will treat the behavioral problems associated with ADHD. The combined administration of the compounds of Formula I and optionally an agonist and the psychostimulant or monoamine reuptake inhibitor is expected to require less of the generally-prescribed dose for either agent when used alone and or is expected to result in less frequent administration of either or both agents. The skilled clinician may in fact learn that behavioral problems are secondary to the cognitive problems and can be treated with lower dosages of the inhibitors. Determining such dosages should be a routine determination by one skilled in the art of treating patients with ADHD.

Mood and affective disorders fall within a large group of diseases, including monopolar depression and bi-polar mood disorder. These diseases are treated with three major classes of compounds. The first group is the heterocyclic antidepressant (HCA's). This group includes the well-known tricyclic antidepressants. The second group of compounds used to treat mood disorders is the monoamine oxidase inhibitors (MAOI's) that are used in particular types of diseases. The third drug is lithium.

Common side effects from HCA's are sedation and weight gain. In elderly patients with organic brain disease, the side effects of HCA's can also include seizures and behavioral symptoms. The main side effects from using MAOI's occur from dietary and drug interactions. Benign side effects from the use of lithium include, but are not limited to, weight gain, nausea, diarrhea, polyuria, polydipsia, and tremor. Toxic side effects from lithium can include persistent headache, mental confusion, and may reach seizures and cardiac arrhythmias. Therefore, agents with less side effects or interactions with food or other medications would be useful.

Depression is a mood disorder of varying lengths of normally several months to more than two years and of varying degrees of feelings involving sadness, despair, and discouragement. The heterocyclic antidepressants (HCA's) are currently the largest class of antidepressants, but monoamine oxidase inhibitors (MAOI's) are used in particular types of depression. Common side effects from HCA's are sedation and weight gain. In elderly patients with organic brain disease, the side effects from HCA's can also include seizures and behavioral symptoms. The main side effects from using MAOI's occur from dietary and drug interactions. Therefore, agents with fewer side effects would be useful.

Borderline personality disorder, although not as well known as bipolar disorder, is more common. People having borderline personality disorder suffer from a disorder of emotion regulation. Pharmaceutical agents are used to treat specific symptoms, such as depression or thinking distortions.

Acquired immune deficiency syndrome (AIDS) results from an infection with the human immunodeficiency virus (HIV). This virus attacks selected cells and impairs the proper function of the immune, nervous, and other systems. HIV infection can cause other problems such as, but not limited to, difficulties in thinking, otherwise known as AIDS dementia complex. Therefore, there is a need to drugs to relieve the confusion and mental decline of persons with AIDS.

Amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, belongs to a class of disorders known as motor neuron diseases wherein specific nerve cells in the brain and spinal cord gradually degenerate to negatively affect the control of voluntary movement. Currently, there is no cure for amyotrophic lateral sclerosis although patients may receive treatment from some of their symptoms and although

Riluzole has been shown to prolong the survival of patients. Therefore, there is a need for a pharmaceutical agent to treat this disease.

Traumatic brain injury occurs when the brain is damaged from a sudden physical assault on the head. Symptoms of the traumatic brain injury include
5 confusion and other cognitive problems. Therefore, there is a need to address the symptoms of confusion and other cognitive problems.

Brain tumors are abnormal growths of tissue found inside of the skull. Symptoms of brain tumors include behavioral and cognitive problems. Surgery, radiation, and chemotherapy are used to treat the tumor, but other agents are necessary
10 to address associated symptoms. Therefore, there is a need to address the symptoms of behavioral and cognitive problems.

Persons with Down's syndrome have in all or at least some of their cells an extra, critical portion of the number 21 chromosome. Adults who have Down's syndrome are known to be at risk for Alzheimer-type dementia. Currently, there is no
15 proven treatment for Down's syndrome. Therefore, there is a need to address the dementia associated with Down's syndrome.

Genetically programmed degeneration of neurons in certain areas of the brain cause Huntington's disease. Early symptoms of Huntington's disease include mood swings, or trouble learning new things or remembering a fact. Most drugs used to
20 treat the symptoms of Huntington's disease have side effects such as fatigue, restlessness, or hyperexcitability. Currently, there is no treatment to stop or reverse the progression of Huntington's disease. Therefore, there is a need of a pharmaceutical agent to address the symptoms with fewer side effects.

General anxiety disorder (GAD) occurs when a person worries about things
25 such as family, health, or work when there is no reason to worry and is unable not to worry. About 3 to 4% of the U.S. population has GAD during the course of a year. GAD most often strikes people in childhood or adolescence, but can begin in adulthood, too. It affects women more often than men. Currently, treatment involves cognitive-behavioral therapy, relaxation techniques, and biofeedback to control
30 muscle tension and medications such as benzodiazepines, imipramine, and buspirone. These drugs are effective but all have side-effect liabilities. Therefore, there is a need of a pharmaceutical agent to address the symptoms with fewer side effects.

Dementia with Lewy Bodies is a neurodegenerative disorder involving abnormal structures known as Lewy bodies found in certain areas of the brain. Symptoms of dementia with Lewy bodies include, but are not limited to, fluctuating cognitive impairment with episodic delirium. Currently, treatment concerns
5 addressing the parkinsonian and psychiatric symptoms. However, medicine to control tremors or loss of muscle movement may actually accentuate the underlying disease of dementia with Lewy bodies. Therefore, there is a need of a pharmaceutical agent to treat dementia with Lewy bodies.

Age-related macular degeneration (AMD) is a common eye disease of the
10 macula which is a tiny area in the retina that helps produce sharp, central vision required for "straight ahead" activities that include reading and driving. Persons with AMD lose their clear, central vision. AMD takes two forms: wet and dry. In dry AMD, there is a slow breakdown of light-sensing cells in the macula. There currently is no cure for dry AMD. In wet AMD, new, fragile blood vessels growing beneath the
15 macula as dry AMD worsens and these vessels often leak blood and fluid to cause rapid damage to the macula quickly leading to the loss of central vision. Laser surgery can treat some cases of wet AMD. Therefore, there is a need of a pharmaceutical agent to address AMD.

Parkinson's disease is a neurological disorder characterized by tremor,
20 hypokinesia, and muscular rigidity. Currently, there is no treatment to stop the progression of the disease. Therefore, there is a need of a pharmaceutical agent to address Parkinson's.

Tardive dyskinesia is associated with the use of conventional antipsychotic drugs. This disease is characterized by involuntary movements most often manifested
25 by puckering of the lips and tongue and/or writhing of the arms or legs. The incidence of tardive dyskinesia is about 5% per year of drug exposure among patients taking conventional antipsychotic drugs. In about 2% of persons with the disease, tardive dyskinesia is severely disfiguring. Currently, there is no generalized treatment for tardive dyskinesia. Furthermore, the removal of the effect-causing drugs is not always
30 an option due to underlying problems. Therefore, there is a need for a pharmaceutical agent to address the symptoms of tardive dyskinesia.

Pick's disease results from a slowly progressive deterioration of social skills and changes in personality with the resulting symptoms being impairment of intellect,

memory, and language. Common symptoms include memory loss, lack of spontaneity, difficulty in thinking or concentrating, and speech disturbances. Currently, there is no specific treatment or cure for Pick's disease but some symptoms can be treated with cholinergic and serotonin-boosting antidepressants. In addition, antipsychotic medications may alleviate symptoms in FTD patients who are experiencing delusions or hallucinations. Therefore, there is a need for a pharmaceutical agent to treat the progressive deterioration of social skills and changes in personality and to address the symptoms with fewer side effects.

Post-traumatic stress disorder (PTSD) is a form of anxiety triggered by memories of a traumatic event that directly affected the patient or that the patient may have witnessed. The disorder commonly affects survivors of traumatic events including sexual assault, physical assault, war, torture, natural disasters, an automobile accident, an airplane crash, a hostage situation, or a death camp. The affliction also can affect rescue workers at an airplane crash or a mass shooting, someone who witnessed a tragic accident or someone who has unexpectedly lost a loved one. Treatment for PTSD includes cognitive-behavioral therapy, group psychotherapy, and medications such as Clonazepam, Lorazepam and selective serotonin-reuptake inhibitors such as Fluoxetine, Sertraline, Paroxetine, Citalopram and Fluvoxamine. These medications help control anxiety as well as depression. Various forms of exposure therapy (such as systemic desensitization and imaginal flooding) have all been used with PTSD patients. Exposure treatment for PTSD involves repeated reliving of the trauma, under controlled conditions, with the aim of facilitating the processing of the trauma. Therefore, there is a need for better pharmaceutical agents to treat Post traumatic stress disorder.

Dysregulation of food intake associated with eating disease, including bulimia nervosa and anorexia nervosa, involve neurophysiological pathways. Anorexia nervosa is hard to treat due to patients not entering or remaining in after entering programs. Currently, there is no effective treatment for persons suffering from severe anorexia nervosa. Cognitive behavioral therapy has helped patients suffering from bulimia nervosa; however, the response rate is only about 50% and current treatment does not adequately address emotional regulation. Therefore, there is a need for pharmaceutical agents to address neurophysiological problems underlying diseases of dysregulation of food intake.

Cigarette smoking has been recognized as a major public health problem for a long time. However, in spite of the public awareness of health hazard, the smoking habit remains extraordinarily persistent and difficult to break. There are many treatment methods available, and yet people continue to smoke. Administration of nicotine transdermally, or in a chewing gum base is common treatments. However, nicotine has a large number of actions in the body, and thus can have many side effects. It is clear that there is both a need and a demand of long standing for a convenient and relatively easy method for aiding smokers in reducing or eliminating cigarette consumption. A drug that could selectively stimulate only certain of the nicotinic receptors would be useful in smoke cessation programs.

Smoke cessation programs may involve oral dosing of the drug of choice. The drug may be in the form of tablets. However, it is preferred to administer the daily dose over the waking hours, by administration of a series of incremental doses during the day. The preferred method of such administration is a slowly dissolving lozenge, troche, or chewing gum, in which the drug is dispersed. Another drug in treating nicotine addiction is Zyban. This is not a nicotine replacement, as are the gum and patch. Rather, this works on other areas of the brain, and its effectiveness is to help control nicotine craving or thoughts about cigarette use in people trying to quit. Zyban is not very effective and effective drugs are needed to assist smokers in their desire to stop smoking. These drugs may be administered transdermally through the use of skin patches. In certain cases, the drugs may be administered by subcutaneous injection, especially if sustained release formulations are used.

Drug use and dependence is a complex phenomenon, which cannot be encapsulated within a single definition. Different drugs have different effects, and therefore different types of dependence. Drug dependence has two basic causes, that is, tolerance and physical dependence. Tolerance exists when the user must take progressively larger doses to produce the effect originally achieved with smaller doses. Physical dependence exists when the user has developed a state of physiologic adaptation to a drug, and there is a withdrawal (abstinence) syndrome when the drug is no longer taken. A withdrawal syndrome can occur either when the drug is discontinued or when an antagonist displaces the drug from its binding site on cell receptors, thereby counteracting its effect. Drug dependence does not always require physical dependence.

In addition drug dependence often involves psychological dependence, that is, a feeling of pleasure or satisfaction when taking the drug. These feelings lead the user to repeat the drug experience or to avoid the displeasure of being deprived of the drug. Drugs that produce strong physical dependence, such as nicotine, heroin and alcohol are often abused, and the pattern of dependence is difficult to break. Drugs that produce dependence act on the CNS and generally reduce anxiety and tension; produce elation, euphoria, or other pleasurable mood changes; provide the user feelings of increased mental and physical ability; or alter sensory perception in some pleasurable manner. Among the drugs that are commonly abused are ethyl alcohol, opioids, anxiolytics, hypnotics, cannabis (marijuana), cocaine, amphetamines, and hallucinogens. The current treatment for drug-addicted people often involves a combination of behavioral therapies and medications. Medications, such as methadone or LAAM (levo-alpha-acetyl-methadol), are effective in suppressing the withdrawal symptoms and drug craving associated with narcotic addiction, thus reducing illicit drug use and improving the chances of the individual remaining in treatment. The primary medically assisted withdrawal method for narcotic addiction is to switch the patient to a comparable drug that produces milder withdrawal symptoms, and then gradually taper off the substitute medication. The medication used most often is methadone, taken orally once a day. Patients are started on the lowest dose that prevents the more severe signs of withdrawal and then the dose is gradually reduced. Substitutes can be used also for withdrawal from sedatives. Patients can be switched to long-acting sedatives, such as diazepam or phenobarbital, which are then gradually reduced.

Gilles de la Tourette's Syndrome is an inherited neurological disorder. The disorder is characterized by uncontrollable vocal sounds called tics and involuntary movements. The symptoms generally manifest in an individual before the person is 18 years of age. The movement disorder may begin with simple tics that progress to multiple complex tics, including respiratory and vocal ones. Vocal tics may begin as grunting or barking noises and evolve into compulsive utterances. Coprolalia (involuntary scatologic utterances) occurs in 50% of patients. Severe tics and coprolalia may be physically and socially disabling. Tics tend to be more complex than myoclonus, but less flowing than choreic movements, from which they must be differentiated. The patient may voluntarily suppress them for seconds or minutes.

Currently simple tics are often treated with benzodiazepines. For simple and complex tics, Clonidine may be used. Long-term use of Clonidine does not cause tardive dyskinesia; its limiting adverse effect is hypotension. In more severe cases, antipsychotics, such as Haloperidol may be required, but side effects of dysphoria,
5 parkinsonism, akathisia, and tardive dyskinesia may limit use of such antipsychotics. There is a need for safe and effective methods for treating this syndrome.

Glaucoma is within a group of diseases occurs from an increase in intraocular pressure causing pathological changes in the optical disk and negatively affects the field of vision. Medicaments to treat glaucoma either decrease the amount of fluid
10 entering the eye or increase drainage of fluids from the eye in order to decrease intraocular pressure. However, current drugs have drawbacks such as not working over time or causing side effects so the eye-care professional has to either prescribe other drugs or modify the prescription of the drug being used. There is a need for safe and effective methods for treating problems manifesting into glaucoma.

15 Ischemic periods in glaucoma cause release of excitotoxic amino acids and stimulate inducible form of nitric oxide synthase (iNOS) leading to neurodegeneration. A PAM stimulates an agonist to affect the release of inhibitory amino acids such as GABA which will dampen hyperexcitability. PAMs are also directly neuroprotective on neuronal cell bodies. Thus, PAMs have the potential to be
20 neuroprotective in glaucoma.

Persons afflicted with pain often have what is referred to as the "terrible triad" of suffering from the pain, resulting in sleeplessness and sadness, all of which are hard on the afflicted individual and that individual's family. Pain can manifest itself in various forms, including, but not limited to, headaches of all severity, back pain,
25 neurogenic, and pain from other ailments such as arthritis and cancer from its existence or from therapy to irradiate it. Pain can be either chronic (persistent pain for months or years) or acute (short-lived, immediate pain to inform the person of possible injury and need of treatment). Persons suffering from pain respond differently to individual therapies with varying degrees of success. There is a need for
30 safe and effective methods for treating pain.

TNF- α is a pro-inflammatory cytokine secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli (e.g., lipopolysaccharide--LPS) or external cellular stresses (e.g., osmotic shock and

peroxide). Elevated levels of TNF- α over basal levels have been implicated in mediating or exacerbating a number of diseases or conditions involving inflammation, pain, cancer, and diabetes. TNF- α is upstream in the cytokine cascade of inflammation. By decreasing levels of TNF- α , not only are levels of TNF- α minimized, but also elevated levels of other inflammatory and proinflammatory cytokines, such as IL-1, IL-6, and IL-8. TNF- α plays a role in head trauma, stroke, and ischemia. Shohami et al., *J. Cereb. Blood Flow Metab.*, 14, 615 (1994). TNF- α promotes the infiltration of other cytokines (IL-1 β , IL-6) and also chemokines, which promote neutrophil infiltration into the infarct area. TNF- α plays a role in promoting certain viral life cycles and disease states associated with them; for instance, TNF- α secreted by monocytes induced elevated levels of HIV expression in a chronically infected T cell clone. Clouse et al., *J. Immunol.*, 142, 431 (1989); Lahdevirte et al., *Am. J. Med.* 85, 289 (1988). TNF- α is associated with the HIV mediated states of cachexia due to cancer and muscle degradation.

TNF- α plays a role in pancreatic beta cell destruction and diabetes. Yoon JW, and Jun HS, *Diabetologia*, 44(3), 271-285 (2001). Pancreatic beta cells produce insulin which helps mediate blood-glucose homeostasis. Deterioration of pancreatic beta cells often accompanies type I diabetes. Pancreatic beta cell functional abnormalities may occur in patients with type II diabetes. Type II diabetes is characterized by a functional resistance to insulin. Further, type II diabetes is also often accompanied by elevated levels of plasma glucagon and increased rates of hepatic glucose production.

In rheumatoid arthritis, TNF- α induces synoviocytes and chondrocytes to produce collagenase and neutral proteases, which lead to tissue destruction within the arthritic joints. In a model of arthritis (collagen-induced arthritis (CIA) in rats and mice), intra-articular administration of TNF- α either prior to or after the induction of CIA led to an accelerated onset of arthritis and a more severe course of the disease. Brahn et al., *Lymphokine Cytokine Res.*, 11, 253 (1992); and Cooper, *Clin. Exp. Immunol.*, 898, 244 (1992). By reducing TNF- α levels, the resulting levels of synoviocytes and chondrocytes are also reduced to prevent or minimize the effects of rheumatoid arthritis.

The compounds of the present invention are useful to treat, or used to prepare a medicament used to treat, diseases or conditions where a mammal receives

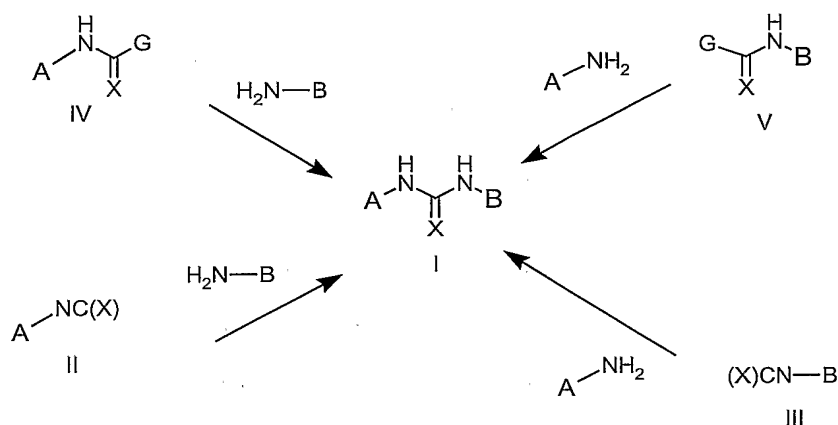
symptomatic relief from the decrease of levels of TNF- α ; these diseases or conditions include, but are not limited to, any one or more or combination of the following: rheumatoid arthritis; rheumatoid spondylitis; muscle degeneration; osteoporosis; osteoarthritis; psoriasis; contact dermatitis; bone resorption diseases; atherosclerosis; 5 Paget's disease; uveitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); Crohn's disease; rhinitis; ulcerative colitis; anaphylaxis; asthma; Reiter's syndrome; tissue rejection of a graft; ischemia reperfusion injury; brain trauma; stroke; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever and myalgias due to infection; HIV-1, HIV- 10 2, or HIV-3; CMV; influenza, adenovirus, a herpes virus (including HSV-1, HSV-2); herpes zoster; multiple myeloma; acute and chronic myelogenous leukemia; cancer-associated cachexia; pancreatic beta cell destruction; type I or type II diabetes.

Some nicotinic receptors regulate vascular angiogenesis; for example, the binding of nicotine to the α -7 nAChR stimulates DNA synthesis and proliferation 15 of vascular endothelial cells. Villablanca, *supra*. The compounds of the present invention are also useful to treat, or are used to prepare a medicament to treat, diseases or conditions where a mammal receives symptomatic relief from the stimulation of vascular angiogenesis; these diseases or conditions include, but not limited to, any one or more of the following: wound healing (healing burns, and wounds in general 20 including from surgery), bone fracture healing, ischemic heart disease, and stable angina pectoris.

Compounds of Formula I can be prepared as shown in Scheme 1. The syntheses shown in the following schemes use intermediates where W^{A-1} , W^{A-2} , W^{A-3} , 25 W^{A-4} , and W^{A-5} for the final compounds would be CR_A . One of ordinary skill in the art could make the corresponding compounds where up to four of W^{A-1} , W^{A-2} , W^{A-3} , W^{A-4} , and W^{A-5} are N making non-critical changes to the methods discussed. The intermediates leading to the B moiety of Formula I can also be prepared by one of ordinary skill in the art with the methods discussed herein or using known procedures 30 or commercially available intermediates. The following discussion is not intended to limit the scope of the invention but is for exemplification only. Methods to synthesize ureas and thioureas of Formula I are well known to one skilled in the art. For example, aryl isocyanates or aryl isothiocyanates (II) or heteroaryl isocyanates or

heteroaryl isothiocyanates (III) can be reacted with aminoheterocycles or anilines to provide the desired urea or thiourea using procedures described in *J. Med. Chem.* **1996**, 39, 304; *J. Med. Chem.* **1999**, 39, 4382; *Pharmazie* **1999**, 54, 19; *J. Chem. Soc.* **1963**, 40, 369; *J. Chem. Soc. Perkin Trans. I* **1977**, 1616; and *Synth. Commun.* **2001**, 31, 781. Alternatively, compounds of formula IV or V can be reacted with an aminoheterocycle or an aniline to provide the desired urea or thiourea using procedures described in *J. Med. Chem.* **1999**, 39, 304; *J. Med. Chem.* (1995) 38, 855.

Scheme 1

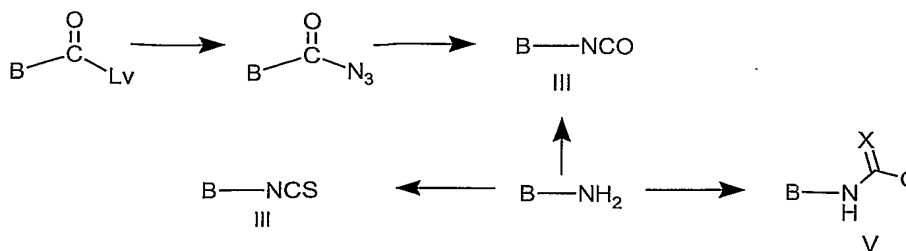


where G is 4-nitro-phenoxy, phenoxy, or imidazol-1-yl.

Compounds of Formula III can be prepared as shown in Scheme 2. Methods to synthesize isocyanates or isothiocyanates of Formula III are well known to one skilled in the art. For example, an aminoheterocycle can be reacted with excess phosgene (or phosgene equivalent) or thiophosgene in refluxing ethyl acetate to provide the heterocyclic isocyanate as described in US 3,759,940. Alternatively, heterocyclic isocyanates III can be prepared from the corresponding carboxylic acid or acid derivative by treatment with an azide source such as sodium azide or diphenylphosphoryl azide (DPPA) followed by a Curtius-type rearrangement using procedures described in *J. Org. Chem.* **1985**, 50, 5723; *J. Org. Chem.* **1997**, 62, 3013.

Compounds of Formula V can be synthesized using procedures well known to one skilled in the art (see DE 1816696; and Greene, T. W. and Wuts, P. G. M. "Protective Groups in Organic Synthesis", 3rd Edition, p. 549, New York:Wiley, (1999)). The requisite aminoheterocycles or heterocyclic carboxylic acids can be obtained from commercial sources or can be synthesized by known procedures.

Scheme 2

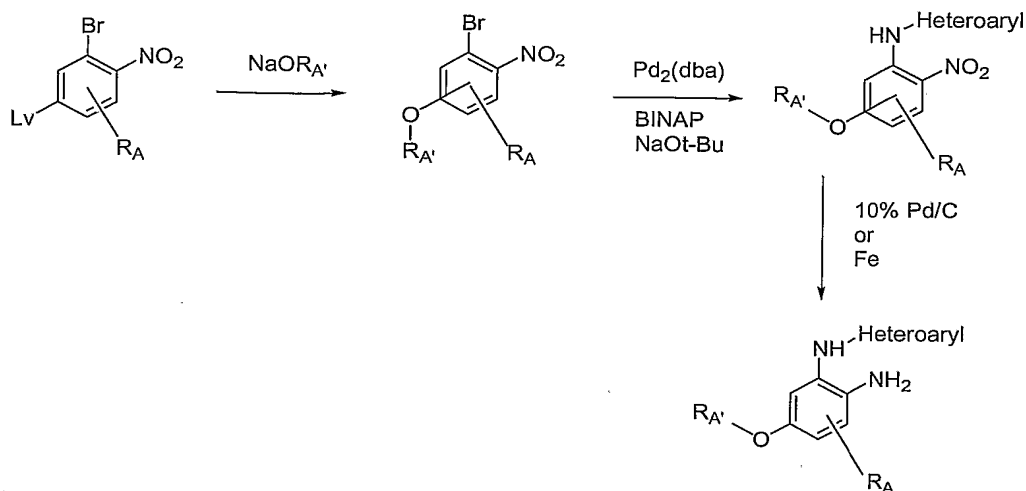


where G is as defined for Scheme 1 and Lv is OH, Cl, or -NH-NH₂.

It will be apparent to those skilled in the art that the aryl isocyanates or aryl isothiocyanates II can be obtained commercially or can be synthesized by known procedures. Compounds of Formula II can be prepared in a manner exactly analogous to the procedures used for the preparation of compounds of Formula III. The requisite substituted anilines can be purchased from commercial sources or prepared using procedures outlined in *J. Org. Chem.* **1997**, 62, 6471. Alternatively, aryl isocyanates II can be prepared from the corresponding carboxylic acid or acid derivative by treatment with an azide source such as sodium azide or diphenylphosphoryl azide (DPPA) followed by a Curtius-type rearrangement using procedures described in *Synth. Commun.* **1993**, 23, 335; or *Heterocycles* **1993**, 36, 1305. Aryl isothiocyanates II can be prepared according to procedures in *J. Org. Chem.* **2000**, 65, 6237.

Heteroaryl amine linked compounds can be prepared via the general route outlined in Scheme 3. A substituted 2-bromo-nitrobenzene is treated with sodium alkoxide to give the O-substituted compound. This is coupled with requisite aminopyridine via a palladium catalysis (see, Yang, B. H. and Buchwald, S. L. *Journal of Organometallic Chem.* **1999**, 576, 125.146.) The nitro group is reduced to its corresponding amine utilizing methods apparent to those skilled in the art and then reacted with either an aryl carbamate or isocyanate as outlined in previous schemes.

Scheme 3

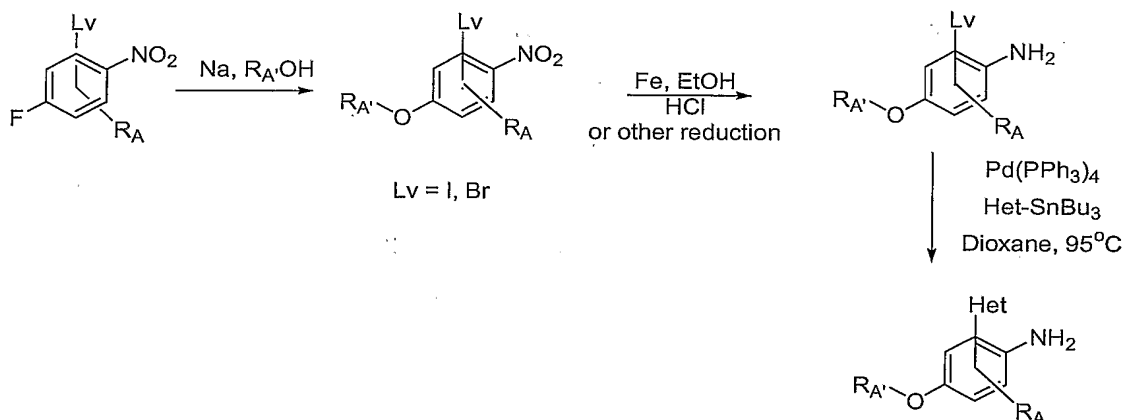


where Lv is F, Cl, Br, SO₂Me.

Heteroaryl linked compounds are prepared via the general route outlined in Scheme 4. A substituted 2-bromo-nitrobenzene is treated with the preformed NaOR to give the alkoxy substituted product, which was reduced to the amine with Fe (powder) or an alternative reduction apparent to one skilled in the art to afford 2-bromo-alkoxy aniline. The Stille coupling of 2-bromo-alkoxy aniline with stannane-heterocycle, which is prepared by the treatment of heterocycle with n-BuLi and tributyltin chloride (Joullie, *Tetrahedron Lett.* **1994**, 35, 7719-22).

10

Scheme 4



Using the procedures discussed herein and the appropriate starting materials that are either commercially available or readily prepared by one of ordinary skill in the art using known procedures, the compounds of formula I can be prepared where R_{A'} is substituted alkyl and R_A is other than H, for example but not limitation, halogen. Furthermore, one of ordinary skill in the art can controlled where the substitution will occur on the phenyl ring of A by selecting the appropriate starting materials as discussed in Schemes 3 and 4.

15

The following examples are provided as examples and are not intended to limit the scope of this invention to only those provided examples and named compounds.

5 **Example 1:** N-[4-ethoxy-2-(pyridin-4-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea.

Absolute EtOH (300mL) is cooled in an ice bath and sodium (2.1 g) is slowly added. The cooling bath is removed and the resulting mixture allowed to stir at ambient temperature for 2 hours. 2-Bromo-4-fluoro-1-nitrobenzene (6.0 g) is slowly
10 added, and the resulting mixture allowed to stir for 15 hours. A solution of citric acid (1.0 M) is added until the pH was ~ 4. Water is added, the volatiles are removed *in vacuo* and the residue taken up in EtOAc, washed with water, brine, dried (Na₂SO₄) and 2-bromo-4-ethoxy-1-nitrobenzene is crystallized from 1-chlorobutane/hexane. Yield 68%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04, 7.40, 7.11, 4.15, 1.33.

15 A mixture of 4-aminopyridine (0.37 g), 2-bromo-4-ethoxy-1-nitrobenzene (1.0 g) Pd₂(bda) (0.15 g), BINAP (0.20 g), and sodium *tert*-butoxide (0.58 g) is purged with argon, then toluene (40 mL) is added and the resulting mixture heated to 85°C for 1 hour and then cooled. The solvent is removed *in vacuo*, and the residue purified using silica gel chromatography (50% to 75% EtOAc/heptane) to give N-(5-ethoxy-2-
20 nitrophenyl)pyridin-4-amine. Yield 84%. MS (ESI+) for C₁₃H₁₃N₃O₃ *m/z* 260.1 (M-H)⁺.

N-(5-ethoxy-2-nitrophenyl)pyridin-4-amine (0.87 g) is suspended in MeOH (~200 mL) and 10% Pd/C (0.27 g) is added. The mixture is shaken under 45 psi H₂ for 30 minutes, filtered and concentrated to give 4-ethoxy-N²-pyridin-4-ylbenzene-
25 1,2-diamine as a solid. Yield 89%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.08, 7.98, 6.71, 6.6-6.5, 4.2, 3.87, 1.26.

4-Ethoxy-N²-pyridin-4-ylbenzene-1,2-diamine ((0.33 g), TEA (0.3 mL) and phenyl 5-methylisoxazol-3-ylcarbamate (0.33 g) are dissolved in THF (10 mL). The resulting suspension is heated to 50°C for 4 hours, and allowed to stir at rt for an
30 additional 12 hours. The solvent is removed *in vacuo* and Example 1 is obtained as solid crystallized from MeCN. Yield 81%. HRMS (ESI) calcd for C₁₈H₁₉N₅O₃+H 354.1566, found 354.1551.

Example 2: N-[4-ethoxy-2-(pyridin-3-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea.

2-Bromo-4-ethoxy-1-nitrobenzene (1.06 g), 3-aminopyridine (0.38 g), Pd₂(bda) (0.15 g), BINAP (0.20 g), and sodium *tert*-butoxide (0.59 g) is purged with argon, then toluene (40 mL) is added and the resulting mixture heated to 85°C for 1 hour and then cooled. The solvent is removed *in vacuo*, and N-(5-ethoxy-2-nitrophenyl)pyridin-3-amine is purified using silica gel chromatography. Yield 77%. MS (CI⁺) for C₁₃H₁₃N₃O₃ *m/z* 260.1 (M+H)⁺.

N-(5-Ethoxy-2-nitrophenyl)pyridin-3-amine (0.79 g) is suspended in MeOH (~200 mL) and 10% Pd/C is added (0.16 g). The mixture is reacted under 45 psi H₂ for 1 hour, filtered and concentrated to give 4-ethoxy-N²-pyridin-3-ylbenzene-1,2-diamine as a solid. Yield 95%. MS (EI) *m/z* (rel intensity) 230 (33), 229 (M⁺, 99), 201 (20), 200 (70), 199 (11), 185 (17), 173 (12), 172 (46), 156 (12), 155 (28).

4-Ethoxy-N²-pyridin-3-ylbenzene-1,2-diamine (0.30 g), TEA (0.28 mL) and phenyl 5-methylisoxazol-3-ylcarbamate (0.32 g) are dissolved in THF (10 mL). The resulting suspension is heated to 50°C for 4 hours, and allowed to stir at rt for an additional 12 hours. The solvent is removed *in vacuo* to give Example 2 as a solid crystallized from EtOAc/hexane. Yield 76%. HRMS (ESI) calcd for C₁₈H₁₉N₅O₃+H 354.1566, found 354.1556.

Example 3: N-[4-ethoxy-2-(pyridin-3-ylamino)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea.

4-Ethoxy-N²-pyridin-3-ylbenzene-1,2-diamine (0.30g), DMAP (~ 10 mg), 2-isocyanato-5-(trifluoromethyl)-1,3,4-thiadiazole (0.29 g) are suspended in 1:1 THF/DMF (10 mL) and heated to 50°C for 4 hours, then cooled ambient temperature for an additional 12 hours. The solvents are removed *in vacuo* and the residue purified by silica gel chromatography (7% [1:9 NH₄OH/MeOH]/CH₂Cl₂ to 10%). Yield 77%. HRMS (ESI) calcd for C₁₇H₁₅N₆O₂SF₃+H 425.1007, found 425.0991.

Example 4: N-[4-ethoxy-2-(pyridin-2-ylamino)phenyl]-N'-(5-methylisoxazol-3-yl)urea.

2-Bromo-4-ethoxy-1-nitrobenzene (1.05 g), 2-aminopyridine (0.39 g) Pd₂(bda) (0.15 g), BINAP (0.20 g), and sodium *tert*-butoxide (0.59 g) is purged with argon,

then toluene (40 mL) is added and the resulting mixture heated to 85°C for 1 hour and then cooled. The solvent is removed *in vacuo*, and N-(5-ethoxy-2-nitrophenyl)pyridin-2-amine is purified using silica gel chromatography. Yield 64%. MS (EI) *m/z* (rel intensity) 259 (M⁺,20), 214 (23), 213 (99), 186 (15), 185 (92), 184 (33), 156 (24), 155 (28), 84 (17), 78 (15).

N-(5-ethoxy-2-nitrophenyl)pyridin-2-amine (0.69 g) is suspended in MeOH (~300 mL) and 10% Pd/C (0.20 g) is added. The mixture is reacted under 45 psi H₂ for 30 minutes. The mixture is filtered and concentrated to give 4-ethoxy-N²-pyridin-2-ylbenzene-1,2-diamine as a solid. Yield quantitative. MS (EI) *m/z* (rel intensity) 230 (18), 229 (M⁺,99), 214 (15), 213 (82), 200 (22), 185 (36), 173 (14), 172 (88), 155 (31), 78 (21).

4-Ethoxy-N²-pyridin-2-ylbenzene-1,2-diamine (0.34 g), TEA (0.34 mL), and phenyl 5-methylisoxazol-3-ylcarbamate (0.36 g) are suspended in THF (10 mL), and heated to 50°C for 4 hours, then allowed to stir for an additional 12 hours. The solvents are removed *in vacuo* and Example 4 is crystallized from EtOAc/hexane. Yield 80%. HRMS (ESI) calcd for C₁₈H₁₉N₅O₃+H 354.1566, found 354.1559.

Example 5: N-[4-methoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-(5-methylisoxazol-3-yl)urea.

To a solution of 2-iodo-4-methoxyaniline, see Lizos, D.; Tripoli, R.; Murphy, J. A. *Chem. Commun.* **2003**, 2732-2733, (0.5 g, 2.0 mol) in 1,4-dioxane (12.5 ml) are added Pd(Ph₃P)₄ (0.231 g, 0.20 mmol) and 2-(tributylstannyl)thiazole (0.90 ml, 2.4 mmol). The reaction mixture is purged with argon and refluxed at 95°C for 5hr. The mixture is concentrated, diluted with Hexanes, extracted with CH₃CN, and concentrated under vacuum. 4-Methoxy-2-(1,3-thiazol-2-yl)aniline is purified by silica gel chromatography (CH₂Cl₂) to afford brown oil 0.340 g (83%). MS (ESI⁺) for C₁₀H₁₀N₂OS *m/z* 207.1 (M+H)⁺.

To a solution of the 4-methoxy-2-(1,3-thiazol-2-yl)aniline (0.17 g, 0.82 mmol) in THF (5.0 ml) are added phenyl 5-methylisoxazol-3-ylcarbamate (0.18 g, 0.82 mmol) and TEA (0.112 ml, 0.82 mmol). The reaction mixture is stirred at 50°C for 3hr. The solution is concentrated under vacuum and Example 5 is triturated with CH₂Cl₂/n-heptane to give a yellow solid 0.134 g (49%). HRMS (ESI) calcd for C₁₅H₁₄N₄O₃S+H 331.0865, found 331.0851.

Example 6: N-[4-methoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea.

To a solution of the 4-methoxy-2-(1,3-thiazol-2-yl)aniline (0.17 g, 0.82 mmol) in THF (5.0 ml) are added 2-isocyanato-5-(trifluoromethyl)-1,3,4-thiadiazole (0.16 g, 0.82 mmol) and 4-dimethylamino pyridine (0.0005 g, 0.04 mmol). The reaction mixture is stirred at 50°C for 3hr. The solution is concentrated under vacuum and the residue is purified by silica gel chromatography (50%EtOAc/n-heptane) followed by the trituration with CH₂Cl₂/n-heptane to give a yellow solid 0.148 g (45%). HRMS (ESI) calcd for C₁₄H₁₀N₅O₂S₂F₃+H 402.0306, found 402.0312.

Example 7: N-[4-methoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-(5-methylisoxazol-3-yl)urea.

To a solution of 2-iodo-4-methoxyaniline (0.6 g, 2.4 mol) in 1,4-dioxane (15.0 ml) are added Pd(Ph₃P)₄ (0.279 g, 0.24 mmol) and 2-(tributylstannyl)-1,3-oxazole (2.0 g, 5.6 mmol). The reaction mixture is purged with argon and refluxed at 95°C for 10hr. The mixture is concentrated, diluted with Hexanes, extracted with CH₃CN, and concentrated under vacuum. The residue is purified by silica gel chromatography (CH₂Cl₂) to afford 4-methoxy-2-(1,3-oxazol-2-yl)aniline as a brown oil 0.224 g (49%). HRMS (ESI) calcd for C₁₀H₁₀N₂O₂+H 191.0820, found 191.0813.

To a solution of the 4-methoxy-2-(1,3-oxazol-2-yl)aniline (0.109 g, 0.57 mmol) in THF (5.0 ml) are added phenyl 5-methylisoxazol-3-ylcarbamate (0.125 g, 0.57 mmol) and TEA (0.078 ml, 0.57 mmol). The reaction mixture is stirred at 50°C for 4hr. The solution is concentrated under vacuum and the residue is purified by silica gel chromatography (20%EtOAc/n-heptane) followed by trituration with CH₂Cl₂/n-heptane to afford Example 7 as a white solid 0.083 g (46%). HRMS (ESI) calcd for C₁₅H₁₄N₄O₄+H 315.1093, found 315.1096.

Example 8: N-[4-methoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea.

To a solution of the 4-methoxy-2-(1,3-oxazol-2-yl)aniline (0.115 g, 0.6 mmol) in THF (5.0 ml) are added 2-isocyanato-5-(trifluoromethyl)-1,3,4-thiadiazole (0.118 g, 0.6 mmol) and 4-dimethylamino pyridine (0.0004 g, 0.03 mmol). The reaction

mixture is stirred at 50°C for 4hr. The solution is concentrated under vacuum and the residue is purified by silica gel chromatography (50%EtOAc / n-heptane) followed by the trituration with CH₂Cl₂ / n-heptane to afford a white solid 0.05 g (21%). HRMS (ESI) calcd for C₁₄H₁₀N₅O₃SF₃+H 386.0534, found 386.0551.

5

Example 9: N-[2-(2-furyl)-4-methoxyphenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea.

To a solution of 2-iodo-4-methoxyaniline (0.42 g, 1.68 mmol) in 1,4-dioxane (8.0 ml) are added Pd(Ph₃P)₄ (0.195 g, 0.168 mmol) and 2-(tributylstannyl)furan (0.63 ml, 2.0 mmol). The reaction mixture is purged with argon and refluxed at 95°C for 3hr. The mixture is concentrated, diluted with hexane, extracted with CH₃CN, and concentrated under vacuum. The residue is purified by silica gel chromatography (CH₂Cl₂) to afford 2-(2-furyl)-4-methoxyaniline as brown semi-solid 0.227 g (71%). HRMS (EI) calcd for C₁₁H₁₀NO₂ 189.0790, found 189.0794.

To a solution of the 2-(2-furyl)-4-methoxyaniline (0.06 g, 0.32 mmol) in THF (3.0 ml) are added 2-isocyanato-5-(trifluoromethyl)-1,3,4-thiadiazole (0.075 g, 0.384 mmol) and 4-dimethylamino pyridine (0.0002 g, 0.016 mmol). The reaction mixture is stirred at 50°C for 3hr. The solution is concentrated under vacuum and the residue is purified by silica gel chromatography (30%EtOAc / n-heptane) followed by the trituration with CH₂Cl₂ / n-heptane to afford Example 9 as a white solid 0.04 g (33%). HRMS (ESI) calcd for C₁₅H₁₁N₄O₃SF₃+H 385.0582, found 385.0582.

Example 10: N-[2-(2-furyl)-4-methoxyphenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea.

To a solution of 2-(2-furyl)-4-methoxyaniline (2.4 g, 12.7 mmol) in CH₂Cl₂ (400 ml) is added dropwise, phenyl chloroformate (2.0 ml, 15.2 mmol) and pyridine (1.0 ml, 12.7 mmol) at 0°C. The reaction mixture is stirred at 0°C for 30 min. The solution is washed with 0.1 N HCl, 5 % NaHCO₃, brine, and concentrated under vacuum. The resulting solid is washed with cold EtOAc to give phenyl 2-(2-furyl)-4-methoxyphenylcarbamate as a white solid 2.63 g (67%). MS (ESI+) for C₁₈H₁₅NO₄ m/z 310.2 (M+H)⁺.

To a solution of phenyl 2-(2-furyl)-4-methoxyphenylcarbamate (0.250 g, 0.8 mmol) in THF (10 ml) are added 3-(trifluoromethyl)isoxazol-5-amine (0.121 g, 0.8

mmol) and NaH 60% dispersion in mineral oil (0.032 g, 0.8 mmol). The reaction mixture is stirred at 50°C for 15min. The solution is concentrated under vacuum and the residue is purified by silica gel chromatography (10%EtOAc/CH₂Cl₂) followed by trituration with CH₂Cl₂/hexanes to afford Example 10 as a white solid 0.143 g (48%).
5 MS (ESI+) for C₁₆H₁₂F₃N₃O₄ *m/z* 366.3 (M+H)⁺.

Example 11: N-[4-ethoxy-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea.

To a solution of 2-bromo-4-ethoxy-1-nitrobenzene (2.0 g, 8.13 mmol) in EtOH
10 (38 ml) and HC (1.0 ml) is added Fe (powder) (6.9 g, 121.9 mmol). The reaction mixture is refluxed at 80°C for 1hr. The suspension is filtered through cellulose and washed with EtOH. To this solution DOWEX 50WX2-400 ion exchange resin (16 g) is added; the mixture is allowed to spin submerged in a water bath (35-40°C) on a rotary evaporator for 20 minutes. The mixture is filtered, and the resin washed with
15 EtOH. The product is liberated from the resin by treatment with a solution of 20% NH₄OH/MeOH. The basic alcohol washes are concentrated *in vacuo* to give 2-bromo-4-ethoxyaniline as a brown oil 1.4 g (80%). MS (ESI+) for C₈H₁₀BrNO *m/z* 217.9 (M+H)⁺.

To a solution of 2-bromo-4-ethoxyaniline (4.3 g, 19.9 mol) in 1,4-dioxane
20 (100 ml) are added Pd(Ph₃P)₄ (2.3 g, 1.99 mmol) and 2-(tributylstannyl)furan (7.5 ml, 23.9 mmol). The reaction mixture is refluxed at 95°C for 3hr. The mixture is concentrated, diluted with hexane, extracted with CH₃CN, and concentrated under vacuum. The residue is purified by silica gel chromatography (CH₂Cl₂) to afford 4-ethoxy-2-(2-furyl)aniline as a brown oil 2.5 g (63%). MS (ESI+) for C₁₂H₁₃NO₂ *m/z*
25 204.0 (M+H)⁺.

To a solution of the 4-ethoxy-2-(2-furyl)aniline (0.106 g, 0.52 mmol) in THF
(5.0 ml) are added 2-isocyanato-5-(trifluoromethyl)-1,3,4-thiadiazole (0.102 g, 0.52 mmol) and NaH 60% dispersion in mineral oil (0.020 g, 0.52 mmol). The reaction mixture is stirred at 50°C for 6hr. The solution is concentrated under vacuum and the
30 residue is triturated with CH₂Cl₂ to afford Example 11 as a white solid 0.086 g (42%). HRMS (ESI) calcd for C₁₆H₁₃N₄O₃SF₃+H 399.0739, found 399.0744.

Example 12: N-[4-ethoxy-2-(2-furyl)phenyl]-N'-(5-methylisoxazol-3-yl)urea.

To a solution of the 4-ethoxy-2-(2-furyl)aniline (0.100 g, 0.49 mmol) in THF (5.0 ml) are added phenyl 5-methylisoxazol-3-ylcarbamate (0.129 g, 0.49 mmol) and TEA (0.067 ml, 0.49 mmol). The reaction mixture is stirred at 50°C for 6hr. The solution is concentrated under vacuum and the residue is triturated with CH₂Cl₂ to afford a white solid 0.046 g (28%). HRMS (ESI) calcd for C₁₇H₁₇N₃O₄+H 328.1297, found 328.1295.

Example 13: N-(4-methoxy-2-thien-2-ylphenyl)-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea.

To a solution of 2-iodo-4-methoxyaniline (0.3 g, 1.02 mol) in 1,4-dioxane (7.5 ml) are added Pd(Ph₃P)₄ (0.138 g, 0.12 mmol) and tributyl(thien-2-yl)stannane (0.46 ml, 1.45 mmol). The reaction mixture is purged with argon and refluxed at 95°C for 6hr. The mixture is concentrated, diluted with Hexanes, extracted with CH₃CN, and concentrated under vacuum. The residue is purified by silica gel chromatography (CH₂Cl₂) to afford 4-methoxy-2-thien-2-ylaniline as a brown oil 0.115 g (47%). MS (ESI+) for C₁₁H₁₁NOS *m/z* 206.1 (M+H)⁺.

To a solution of 4-methoxy-2-thien-2-ylaniline (0.09 g, 0.44 mmol) in THF (5.0 ml) are added 2-isocyanato-5-(trifluoromethyl)-1,3,4-thiadiazole (0.102 g, 0.52 mmol) and 4-dimethylamino pyridine (0.00027 g, 0.022 mmol). The reaction mixture is stirred at 50°C for 2hr. The solution is concentrated under vacuum and the residue is triturated with CH₂Cl₂ to afford Example 13 as a white solid 0.1 g (57%). HRMS (ESI) calcd for C₁₅H₁₁N₄O₂S₂F₃ + H 401.0354, found 401.0362.

Example 14: N-[2,4-dimethoxy-5-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea.

To a cooled (-65°C) solution of oxazole (0.54 g) in THF (100 mL) is added drop-wise, a solution of 1.5 M nBuLi in pentane (5.7 mL) over a 5-minute period. The resulting solution is stirred for 35 minutes at -65°C at which time, a solution of tributyltin chloride (2.4 mL) in THF (10 mL) is added drop-wise, and the resulting solution is allowed to warm to 0°C. Several drops of water are added, and the solvent removed *in vacuo* to give 2-(tributylstannyl)-1,3-oxazole that is taken up in Et₂O, washed with saturated KF, brine, dried (Na₂SO₄), and concentrated to give an oil that is carried crude.

5-Bromo-2,4-dimethoxyaniline (0.51 g), 2-(tributylstannyl)-1,3-oxazole (2.7 g), and $\text{Pd}(\text{Ph}_3\text{P})_4$ (0) (0.11 g) are dissolved in dioxane (10 mL) and heated to 95°C for 3 hours. The solvent removed *in vacuo* to give a residue that is taken up in EtOAc, washed with saturated KF, brine, dried (Na_2SO_4), purified by silica gel chromatography to give 2,4-dimethoxy-5-(1,3-oxazol-2-yl)aniline. Yield 58%. MS (ESI+) for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3$ m/z 221.1 ($\text{M}+\text{H}$)⁺.

2,4-Dimethoxy-5-(1,3-oxazol-2-yl)aniline (0.14 g), DMAP (~10 mg), and 2-isocyanato-5-(trifluoromethyl)-1,3,4-thiadiazole (0.12 g) are suspended in 1:1 THF/DMF (10 mL) and heated to 50°C for 4 hours, then cooled ambient temperature for an additional 12 hours. The solvents are removed *in vacuo* and the residue is crystallized from MeCN to give Example 14 as a white solid. Yield 34%. MS (ESI+) for $\text{C}_{15}\text{H}_{12}\text{F}_3\text{N}_5\text{O}_4\text{S}$ m/z 416.2 ($\text{M}+\text{H}$)⁺.

Example 15: N-[4-ethoxy-2-(2-furyl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea.

Absolute EtOH (700 ml) is cooled in an ice bath and sodium (5.2 g) is slowly added. The cooling bath is removed and the resulting mixture allowed to stir at RT for 2 hours. 2-Bromo-4-fluoro-1-nitrobenzene (15.0 g) is slowly added, and the resulting mixture is allowed to stir for 15 hours. A solution of citric acid (1.0 M) is added until the pH is ~ 4. Water (200 ml) is added, the volatiles are removed *in vacuo* and the residue is taken up in EtOAc, washed with water (2 x 100 ml) and then brine, dried (MgSO_4), and crystallized from 1-chlorobutane/*n*-hexane to give 2-bromo-4-ethoxy-1-nitrobenzene. Yield 88%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.04, 7.40, 7.11, 4.15, 1.33.

To a solution of 2-bromo-4-ethoxy-1-nitrobenzene (2.0 g, 8.13 mmol) in EtOH (38 ml) and HCl (1.0 ml) is added Fe (powder) (6.9 g, 121.9 mmol). The reaction mixture is refluxed at 80°C for 1hr. The suspension is filtered through cellulose and washed with EtOH. To this solution DOWEX 50WX2-400 ion exchange resin (16 g) is added; the mixture is allowed to spin submerged in a water bath (35-40°C) on a rotary evaporator for 20 minutes. The mixture is filtered, and the resin is washed with 3 portions of EtOH. The product is liberated from the resin by treatment with a solution of 20% NH_4OH / MeOH that is applied in 3x100 ml portions. The basic

alcohol washes are concentrated *in vacuo* to give 2-bromo-4-ethoxyaniline as a brown oil 1.4 g (80%). HRMS (ESI) calcd for $C_8H_{10}NOBr+H$ 216.0025, found 216.0031.

To a solution of 2-bromo-4-ethoxyaniline (4.3 g, 19.9 mmol) in 1,4-dioxane (100 ml) are added $Pd(Ph_3P)_4$ (2.3 g, 1.99 mmol) and 2-(tributylstannyl)furan (7.5 ml, 23.8 mmol). The reaction mixture is purged with argon and refluxed at 95°C for 2 hr. The mixture is concentrated, diluted with *n*-hexanes, extracted with CH_3CN , and concentrated under vacuum. The residue is purified by silica gel chromatography (CH_2Cl_2) to afford 4-ethoxy-2-(2-furyl)aniline as a brown semi-solid 2.5 g (62%). MS (ESI+) for $C_{12}H_{13}NO_2$ m/z 204.0 ($M+H$)⁺.

To a solution of 4-ethoxy-2-(2-furyl)aniline (2.5 g, 12.3 mmol) in CH_2Cl_2 (370 ml) is added dropwise, phenyl chloroformate (1.8 ml, 14.8 mmol) and pyridine (1.0 ml, 12.3 mmol) at 0°C. The reaction mixture is stirred at 0°C for 30 min. The solution is washed with 0.1 N HCl, 5 % $NaHCO_3$, brine, and concentrated under vacuum. The resulting solid is recrystallized from EtOAc / *n*-hexanes to give phenyl 4-ethoxy-2-(2-furyl)phenylcarbamate as a white solid 2.9 g (73%). HRMS (ESI) calcd for $C_{19}H_{17}NO_4+H$ 324.1236, found 324.1246.

To a solution of 3-(trifluoromethyl)isoxazol-5-amine (0.152 g, 1.0 mmol) in THF (10 ml) is added NaH 60% dispersion in mineral oil (0.04 g, 1.0 mmol). After stirring the mixture at RT for 15 min phenyl 4-ethoxy-2-(2-furyl)phenylcarbamate (0.323 g, 1.0 mmol) is added and the reaction mixture is heated at 50°C for 1 hour. The mixture is neutralized with 0.1M HCl, extracted with EtOAc, and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue is triturated with CH_2Cl_2 to afford Example 15 as a yellow solid 0.188 g (50%). HRMS (ESI) calcd for $C_{17}H_{14}N_3O_4F_3+H$ 382.1014, found 382.1013.

Example 16: N-[4-methoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea.

To a cooled (-65°C) solution of oxazole (0.54 g) in THF (100 ml) is added dropwise, a solution of 1.5 M *n*BuLi in pentane (5.7 ml) over a 5-minute period. The resulting solution is stirred for 35 minutes at -65°C at which time, a solution of tributyltin chloride (2.4 ml) in THF (10 ml) is added dropwise, and the resulting solution is allowed to warm to 0°C. Several drops of water are added, and the solvent is removed *in vacuo* to give a residue that is taken up in Et_2O , washed with 3 x 50 ml

portions of saturated KF, once with brine, dried (Na_2SO_4), and concentrated to give 2-(tributylstannyl)-1,3-oxazole as an oil.

To a solution of 2-iodo-4-methoxyaniline (6.0 g, 2.4 mmol) in 1,4-dioxane (110 ml) is added $\text{Pd}(\text{Ph}_3\text{P})_4$ (2.8 g, 2.4 mmol) and 2-(tributylstannyl)furan (14.3 g, 40.0 mmol). The reaction mixture is purged with argon and refluxed at 95°C for 3 hr. The mixture is concentrated, diluted with *n*-hexanes, extracted with CH_3CN , and concentrated under vacuum. The residue is purified by silica gel chromatography (CH_2Cl_2) to afford 4-methoxy-2-(1,3-oxazol-2-yl)aniline as a brown semi-solid 1.0 g (22%). HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2+\text{H}$ 191.0820, found 191.0813.

To a solution of 4-methoxy-2-(1,3-oxazol-2-yl)aniline (1.0 g, 5.26 mmol) in CH_2Cl_2 (160 ml) is added dropwise, phenyl chloroformate (0.8 ml, 6.3 mmol) and pyridine (0.4 ml, 5.26 mmol) at 0°C . The reaction mixture is stirred at 0°C for 30 min. The solution is washed with 0.1 N HCl, 5 % NaHCO_3 , brine, and concentrated under vacuum. The resulting solid is recrystallized from EtOAc / *n*-hexanes to give phenyl 4-methoxy-2-(1,3-oxazol-2-yl)phenylcarbamate as a white solid 0.827 g (51%). HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4+\text{H}$ 311.1031, found 311.1038.

To a solution of 3-(trifluoromethyl)isoxazol-5-amine (0.08 g, 0.55 mmol) in DMF (10 ml) is added NaH 60% dispersion in mineral oil (0.02 g, 0.55 mmol). After stirring the mixture at RT for 15 min phenyl 4-methoxy-2-(1,3-oxazol-2-yl)phenylcarbamate (0.17 g, 0.55 mmol) is added and the reaction mixture is heated at 50°C for 30 min. The mixture is neutralized with 0.1M HCl, extracted with EtOAc, and the combined organic layers are dried (MgSO_4), filtered, and concentrated under vacuum. The residue is triturated with CH_2Cl_2 / *n*-hexanes to afford Example 16 as a white solid 0.131 g (65%). HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{11}\text{N}_4\text{O}_4\text{F}_3+\text{H}$ 369.0811, found 369.0803.

Example 17: N-[4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea.

To a solution of 2-bromo-4-ethoxyaniline (4.0 g, 18.5 mmol) in 1,4-dioxane (80 ml) is added $\text{Pd}(\text{Ph}_3\text{P})_4$ (2.1 g, 1.85 mmol) and 2-(tributylstannyl)-1,3-oxazole (21.2 g, 59.3 mmol). The reaction mixture is purged with argon and refluxed at 95°C for 3 hr. The mixture is concentrated, diluted with *n*-hexanes, extracted with CH_3CN , and concentrated under vacuum. The residue is purified by silica gel chromatography

(CH₂Cl₂) to afford 4-ethoxy-2-(1,3-oxazol-2-yl)aniline as a brown solid 1.65 g (45%). HRMS (ESI) calcd for C₁₁H₁₂N₂O₂+H 205.0977, found 205.0973.

To a solution of 4-ethoxy-2-(1,3-oxazol-2-yl)aniline (0.8 g, 3.9 mmol) in CH₂Cl₂ (125 ml) is added dropwise, phenyl chloroformate (0.6 ml, 4.7 mmol) and pyridine (0.3 ml, 3.9 mmol) at 0°C. The reaction mixture is stirred at 0°C for 30 min. The solution is washed with 0.1 N HCl, 5 % NaHCO₃, brine, and concentrated under vacuum. The resulting solid is recrystallized from EtOAc to give phenyl 4-ethoxy-2-(1,3-oxazol-2-yl)phenylcarbamate as an off white solid 0.88 g (69%). HRMS (ESI) calcd for C₁₈H₁₆N₂O₄+H 325.1188, found 325.1187.

To a solution of 3-(trifluoromethyl)isoxazol-5-amine (0.047 g, 0.308 mmol) in DMF (6.0 ml) is added NaH 60% dispersion in mineral oil (0.012 g, 0.308 mmol). After stirring the mixture at RT for 15 min phenyl 4-ethoxy-2-(1,3-oxazol-2-yl)phenylcarbamate (0.1 g, 0.308 mmol) is added and the reaction mixture is heated at 50°C for 30 min. The mixture is neutralized with 0.1M HCl, extracted with EtOAc, and the combined organic layers are dried (MgSO₄), filtered, and concentrated under vacuum. The residue is purified by silica gel chromatography (40%EtOAc / heptane) followed by the trituration with CH₂Cl₂ / heptane to afford Example 17 as a white solid 0.103 g (87%). HRMS (ESI) calcd for C₁₆H₁₃N₄O₄F₃+H 383.0967, found 383.0961.

Example 18: N-[4-ethoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea.

To a solution of 2-bromo-4-ethoxyaniline (2.0 g, 9.2 mol) in 1,4-dioxane (40 ml) is added Pd(Ph₃P)₄ (1.0 g, 0.92 mmol) and 2-(tributylstannyl)-1,3-thiazole (4.15 g, 11.1 mmol). The reaction mixture is purged with argon and refluxed at 95°C for 2hr. The mixture is concentrated, diluted with *n*-hexanes, extracted with CH₃CN, and concentrated under vacuum. The residue is purified by silica gel chromatography (CH₂Cl₂) to afford 4-ethoxy-2-(1,3-thiazol-2-yl)aniline as a brown oil 0.809 g (40%). HRMS (ESI) calcd for C₁₁H₁₂N₂OS+H 221.0749, found 221.0745.

To a solution of 4-ethoxy-2-(1,3-thiazol-2-yl)aniline (0.77 g, 3.5 mmol) in CH₂Cl₂ (105 ml) is added dropwise, phenyl chloroformate (0.5 ml, 4.1 mmol) and pyridine (0.28 ml, 3.5 mmol) at 0°C. The reaction mixture is stirred at 0°C for 30 min. The solution is washed with 0.1 N HCl, 5 % NaHCO₃, brine, and concentrated

under vacuum. The resulting solid is recrystallized from EtOAc to give phenyl 4-ethoxy-2-(1,3-thiazol-2-yl)phenylcarbamate as an off white solid 0.78 g (66%).

HRMS (ESI) calcd for $C_{18}H_{16}N_2O_3S+H$ 341.0960, found 341.0956.

To a solution of 3-(trifluoromethyl)isoxazol-5-amine (0.112 g, 0.735 mmol) in THF (5.0 ml) are added phenyl 4-ethoxy-2-(1,3-thiazol-2-yl)phenylcarbamate (0.25 g, 0.735 mmol) and TEA (0.2 ml, 1.5 mmol). The reaction mixture is stirred at 50°C for 2hr. Then NaH 60% dispersion in mineral oil (0.03 g, 0.735 mmol) is added and reaction mixture is stirred at RT for 15 min. The mixture is neutralized with 0.1M HCl, extracted with EtOAc, and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue is triturated with CH_2Cl_2 / heptane to afford Example 18 as an orange solid 0.177 g (61%). HRMS (ESI) calcd for $C_{16}H_{13}N_4O_3SF_3+H$ 399.0739, found 399.0742.

Example 19: N-[4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea.

To a solution of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (0.13 g, 0.77 mmol) in THF (5.0 ml) are added phenyl 4-ethoxy-2-(1,3-oxazol-2-yl)phenylcarbamate (0.25 g, 0.77 mmol) and TEA (0.209 ml, 1.54 mmol). The reaction mixture is stirred at 50°C for 2hr. Then NaH 60% dispersion in mineral oil (0.031 g, 0.77 mmol) is added and reaction mixture is stirred at RT for 15 min. The mixture is neutralized with 0.1M HCl, extracted with EtOAc, and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue is purified by silica gel chromatography (10%EtOAc / CH_2Cl_2) followed by the trituration with CH_2Cl_2 to afford Example 19 as a white solid 0.098 g (32%). HRMS (ESI) calcd for $C_{15}H_{12}N_5O_3SF_3+H$ 400.0691, found 400.0692.

Example 20: N-[4-ethoxy-2-(1,3-thiazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea.

To a solution of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (0.099 g, 0.588 mmol) in THF (5.0 ml) are added phenyl 4-ethoxy-2-(1,3-thiazol-2-yl)phenylcarbamate (0.2 g, 0.588 mmol) and TEA (0.159 ml, 1.176 mmol). The reaction mixture is stirred at 50°C for 2hr. Then NaH 60% dispersion in mineral oil (0.024 g, 0.588 mmol) is added and reaction mixture is stirred at RT for 15 min. The mixture is neutralized with 0.1M HCl, extracted with EtOAc, and the combined

organic layers are dried (MgSO_4), filtered, and concentrated under vacuum. The residue is triturated with EtOAc / heptane to afford Example 20 as an off white solid 0.133 g (55%). HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{12}\text{N}_5\text{O}_2\text{S}_2\text{F}_3+\text{H}$ 416.0463, found 416.0469.

5

Example 21: N-(6-cyanopyridin-3-yl)-N'-[4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]urea.

To a solution of 4-ethoxy-2-(1,3-oxazol-2-yl)aniline (0.204 g, 1.0 mmol) in THF (5.0 ml) are added phenyl 6-cyanopyridin-3-ylcarbamate (0.239 g, 1.0 mmol) and TEA (0.135 ml, 1.0 mmol). The reaction mixture is stirred at 50°C for 2hr. The formed precipitate is filtered to give Example 21 as an off white solid 0.197 g (56%). HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{15}\text{N}_5\text{O}_3+\text{H}$ 350.1253, found 350.1269.

Example 22: N-[2-(1,3-oxazol-2-yl)phenyl]-N'-[3-(trifluoromethyl)isoxazol-5-yl]urea.

To a solution of 2-iodoaniline (1.0 g, 4.56 mmol) in 1,4-dioxane (18 ml) is added $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.527 g, 0.456 mmol) and 2-(tributylstannyl)-1,3-oxazole (17.8 g, 49.7 mmol). The reaction mixture is purged with argon and refluxed at 95°C for 2hr. The mixture is concentrated, diluted with *n*-hexanes, extracted with CH_3CN , and concentrated under vacuum. The residue is purified by silica gel chromatography (CH_2Cl_2) to afford 2-(1,3-oxazol-2-yl)aniline as a brown solid 0.587 g (80%). MS (ESI+) for $\text{C}_9\text{H}_8\text{N}_2\text{O}$ m/z 161.1 ($\text{M}+\text{H}$)⁺.

To a solution of 3-(trifluoromethyl)isoxazol-5-amine (1.0 g, 6.57 mmol) in CH_2Cl_2 (15 ml) is added dropwise, phenyl chloroformate (1.8 ml, 14.45 mmol) and pyridine (1.0 ml, 13.14 mmol) at 0°C. The reaction mixture is stirred at 0°C for 30 min. The reaction mixture is washed with H_2O and 1% HCl. To the combined organic layers are added pyridine (1.0 ml, 6.57 mmol), H_2O (1.0 ml), and CH_2Cl_2 (20 ml), and the mixture is stirred at RT for 3 hours. The reaction mixture is washed with 0.1N HCl and brine, dried (Na_2SO_4), and concentrated. The residue is recrystallized from *n*-hexanes to give phenyl 3-(trifluoromethyl)isoxazol-5-ylcarbamate as an off white solid 1.3 g (73%). MS (ESI-) for $\text{C}_{11}\text{H}_7\text{F}_3\text{N}_2\text{O}_3$ m/z 271.0 ($\text{M}-\text{H}$)⁻.

To a solution of 2-(1,3-oxazol-2-yl)aniline (0.1 g, 0.622 mmol) in THF (5.0 ml) are added phenyl 3-(trifluoromethyl)isoxazol-5-ylcarbamate (0.169 g, 0.622 mmol) and TEA (0.084 ml, 0.622 mmol). The reaction mixture is stirred at 50°C for

3hr. The residue is purified by silica gel chromatography (20%EtOAc / heptane) to afford Example 22 as a white solid 0.135 g (64%). MS (ESI-) for $C_{14}H_9F_3N_4O_3$ m/z 337.1 (M-H)⁻.

5 **Example 23:** N-[2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea.

To a solution of 2-iodoaniline (1.0 g, 4.56 mol) in 1,4-dioxane (18 ml) is added $Pd(Ph_3P)_4$ (0.527 g, 0.456 mmol) and 2-(tributylstannyl)furan (1.7 g, 5.47 mmol). The reaction mixture is purged with argon and refluxed at 95°C for 2hr. The
10 mixture is concentrated, diluted with *n*-hexanes, extracted with CH_3CN , and concentrated under vacuum. The residue is purified by silica gel chromatography (CH_2Cl_2) to afford 2-(2-furyl)aniline as a brown oil 0.62 g (86%). MS (ESI+) for $C_{10}H_9NO$ m/z 160.0 (M+H)⁺.

To a solution of 2-(2-furyl)aniline (0.25 g, 1.57 mmol) in CH_2Cl_2 (40 ml) is
15 added dropwise, phenyl chloroformate (0.236 ml, 1.88 mmol) and pyridine (0.127 ml, 1.57 mmol) at 0°C. The reaction mixture is stirred at 0°C for 30 min. The solution is washed with 0.1 N HCl, 5 % $NaHCO_3$, brine, and concentrated under vacuum. The resulting solid is recrystallized from EtOAc to give phenyl 2-(2-furyl)phenylcarbamate as an off white solid 0.165 g (38%). HRMS (ESI) calcd for $C_{17}H_{13}NO_3+H$ 280.0974,
20 found 280.0982.

To a solution of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (0.1 g, 0.59 mmol) in THF (5.0 ml) are added phenyl 2-(2-furyl)phenylcarbamate (0.165 g, 0.59 mmol) and TEA (0.08 ml, 0.59 mmol). The reaction mixture is stirred at 50°C for 3hr. The residue is purified by silica gel chromatography (20%EtOAc / heptane) to
25 afford Example 23 as a white solid 0.77 g (85%). MS (ESI-) for $C_{14}H_9F_3N_4O_2S$ m/z 353.0 (M-H)⁻.

Example 24: N-[4-ethoxy-2-(2-furyl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea.

30 3-Methyl-5-phenyl-1,2,4-oxadiazole is prepared according to literature (M.A. Perez, C.A. Dorado, J.L. Soto, Synthesis **1983**, 483-6). Ethyl acetimidate hydrochloride (25.0 g, 202mmol) is stirred in CH_2Cl_2 (400 mL) in a flask under N_2 . The reaction mixture is cooled in an ice water bath and TEA (59.2 mL, 425 mmol) is

added. Benzoyl chloride (23.5 mL, 202 mmol) in CH_2Cl_2 (40 mL) is added dropwise over approximately 30 minutes. After 2 hours, the reaction mixture is removed from the cooling bath and allowed to stir at RT overnight. A 1 mL aliquot of the reaction mixture is filtered, concentrated and analyzed by ^1H NMR to determine whether the reaction is complete. The reaction mixture is poured into hexane (500 mL) and the resulting mixture is filtered and concentrated. The crude product (41.0 g) is found by ^1H NMR analysis to contain ethyl N-benzoylethanidoate (29.2 g) with the balance of the material being largely solvent. Further purification is not done. ^1H NMR (400 MHz, CDCl_3) δ 1.38, 2.06, 4.30, 7.42-7.46, 7.52-7.57, 8.01-8.03.

Hydroxylamine hydrochloride (11.7 g, 168 mmol) is suspended in dry CH_3OH (80 mL) at RT under N_2 . Sodium methoxide (25 wt. % in CH_3OH) (38.4 mL, 168 mmol) is added. Crude ethyl N-benzoylethanidoate (29.2 g, 153 mmol) is diluted with CH_3OH (88 mL) and this solution is added to the reaction mixture by canula over 20 minutes. The reaction mixture warms during the addition. The reaction mixture is stirred at RT under N_2 for 24 hours. The reaction mixture is filtered through a glass frit and the solids are carefully washed with a small volume of CH_3OH . The filtrate is concentrated and the oily residue slowly crystallizes. The crude product is recrystallized from 1:1 $\text{CH}_3\text{OH}:\text{H}_2\text{O}$ to give 3-methyl-5-phenyl-1,2,4-oxadiazole (12.8 g, 40% yield for two steps). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.43, 7.62-7.65, 7.69-7.73, 8.09-8.11.

A solution of 3-methyl-5-phenyl-1,2,4-oxadiazole (2.55 g, 15.9 mmol) and *iso*-propyl trifluoroacetate (3.36 mL, 23.9 mmol) in anhydrous THF (16 mL) is prepared under N_2 at RT. In a second flask, a solution of diisopropylamine (5.13 mL, 36.6 mmol) in anhydrous THF (32 mL) is prepared under N_2 . This solution is cooled to -40°C and *n*-butyl lithium (1.61 M) (21.7 mL, 35.0 mmol) is added over 10 minutes. The solution of LDA is kept at -10°C for 40 minutes and then it is cooled to less than -75°C . The solution of 3-methyl-5-phenyl-1,2,4-oxadiazole and *iso*-propyl trifluoroacetate in THF is added drop wise to the cold LDA solution over 1.25 hours using a syringe and syringe pump. After the addition of reagents is complete, the reaction mixture is maintained at less than -75°C for 1 hour. The reaction mixture is removed from the cooling bath and allowed to warm up to near RT over the course of 1 hour. The reaction mixture is cooled to -40°C and quenched by the addition of 1N aqueous HCl (71 mL). After quenching, the reaction mixture is

concentrated to remove hexane and THF. The residue is partitioned between Et₂O (250 mL) and H₂O (250 mL). The layers are separated and the aqueous layer is extracted with Et₂O (1 x 150 mL, 1 x 100 mL). The combined organic layers are dried (MgSO₄), filtered and concentrated to yield 1,1,1-trifluoro-3-(5-phenyl-1,2,4-oxadiazol-3-yl)propane-2,2-diol (6.64 g), which is used directly in the next reaction without purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.21, 7.63-7.66, 7.70-7.74, 8.10-8.12.

Dry 1,1,1-trifluoro-3-(5-phenyl-1,2,4-oxadiazol-3-yl)propane-2,2-diol (15.9 mmol) is combined with anhydrous DMSO (15 mL) and the resulting mixture is heated at 90 °C for 2 hours. The reaction mixture is partitioned between CH₂Cl₂ (250 mL) and H₂O (250 mL). The layers are separated and the aqueous layer is extracted with CH₂Cl₂ (2 x 100 mL). The combined organic layers are dried (Na₂SO₄), filtered and concentrated. The crude product (5.89 g) is chromatographed (SiO₂ 300 g, eluted with 3:1 hexane:Et₂O) to give N-[5-(trifluoromethyl)isoxazol-3-yl]benzamide (3.15 g, 77% yield for two steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.54-7.58, 7.64-7.68, 7.75, 8.03-8.05, 11.8.

N-[5-(trifluoromethyl)isoxazol-3-yl]benzamide (3.09 g, 12.0 mmol) is suspended in ethylene glycol (12 mL) and the resulting mixture is warmed to 100 °C. Concentrated aqueous HCl (36 %, 11.6 M)(2.6 mL, 30.1 mmol) is added and the mixture is stirred for 9 hours at 100 °C. The reaction mixture is cooled to RT and partitioned between CH₂Cl₂ (100 mL) and 1N NaOH (100 mL). The layers are separated and the aqueous layer is extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers are dried (MgSO₄), filtered and concentrated. The crude product (4.40 g) is chromatographed (SiO₂ 300 g, eluted with 2:1 Et₂O:hexane) to yield 5-trifluoromethyl-3-aminoisoxazole (1.27 g) in 69% yield. ¹H NMR (400 MHz, CDCl₃) δ 6.26.

5-Trifluoromethyl-3-aminoisoxazole (1.52 g, 10.0 mmol) is dissolved in dry CH₂Cl₂ (20 mL). Phenyl chloroformate (1.72 g, 11.0 mmol) is added. While keeping the temperature below RT, pyridine (0.79 g, 10.0 mmol) is added drop wise. The reaction mixture is washed sequentially with H₂O, 1% aqueous HCl and H₂O. The organic layer is dried (Na₂SO₄) and concentrated. The residue is recrystallized from cyclohexane to yield phenyl 5-(trifluoromethyl)isoxazol-3-ylcarbamate as colorless needles (2.56 g, 94% yield).

Example 24 is prepared from phenyl 5-(trifluoromethyl)isoxazol-3-ylcarbamate and phenyl 4-ethoxy-2-(2-furyl)phenylcarbamate (Ex 15) using the methods discussed herein.

5 **Example 25:** N-[4-ethoxy-2-(1,3-oxazol-2-yl)phenyl]-N'-[5-(trifluoromethyl)isoxazol-3-yl]urea.

Example 24 is prepared from phenyl 5-(trifluoromethyl)isoxazol-3-ylcarbamate and phenyl 4-ethoxy-2-(1,3-oxazol-2-yl) phenylcarbamate (Ex 17) using the methods discussed herein.

10

Materials and Methods for identifying binding constants:

Assay for positive allosteric modulators of $\alpha 7$ nAChR.

Both agonist and positive allosteric modulator activity of the $\alpha 7$ nAChR are
15 assayed using a cell-based, calcium flux assay on FLIPR. SHEP-1 cells expressing a novel, mutated form of the $\alpha 7$ nAChR that permitted stable cell surface expression were used for these assays. The details of the mutated form of the $\alpha 7$ nAChR is described in WO 00/73431.

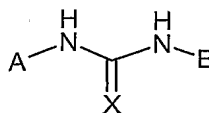
Cells were plated into each well of either a 96 or 384 well cell culture plates,
20 they were transferred to a standard CO₂ incubator for at least 24 h to achieve confluence. The assay described below is for the 96 well assay. The 384-well assay is essentially the same, with the exception that the volumes of the reagents was reduced by a factor of 4. At confluence, the growth media was aspirated and replaced with 200 μ l of new media containing a Calcium Green-1 AM to obtain a final dye
25 concentration was 2 μ M. Cells were incubated for 60 min at 37°C, then washed 4 times leaving 100 μ l of assay buffer in each well. The details of the assay buffer were described in WO 00/73431. At this point, the cell culture plate containing the cells loaded with the calcium indicator dye was placed in FLIPR. FLIPR was configured to excite the Calcium Green at 488 nm and emission was read using a 520 nm filter set.

30 Compounds were prepared as a solutions in an assay buffer. The assay was initiated by collecting 10 baseline data points at 1.5 second intervals. After the baseline points were collected, 100 μ l of compound was added to the well. The resulting 1:1 dilution achieved a final concentration 30 μ M for each compound. An

additional 3 min of data was collected. After 3 min measurements, acetylcholine was added at a final concentration of 100 μ M. Acetylcholine produced a reproducible rapid and transient calcium flux. Positive allosteric modulator activity was defined as a compound that increased the acetylcholine response by greater than 4 standard deviations of the mean response. The examples prepared herein had activity between 10 nM and 10 μ M.

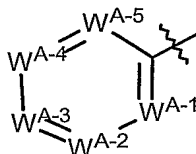
Claims:

1. A compound of Formula I:



wherein X is O or S;

5 A is



wherein each W^{A-1} , W^{A-2} , W^{A-3} , W^{A-4} , and W^{A-5} are independently N or CR_A , provided that no more than four of W^{A-1} , W^{A-2} , W^{A-3} , W^{A-4} , or W^{A-5} are simultaneously N;

10 Each R_A is R_{A-1} or R_{A-2} , provided that one R_A is R_{A-2} ;

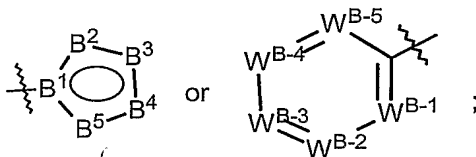
Each R_{A-1} is independently H, halogen, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, aryl, $-N_3$, $-SCN$, $-CN$, $-NO_2$, $-OR_7$, $-SR_8$,
 15 $-S(O)R_8$, $-S(O)_2R_8$, $-N(R_9)_2$, $-C(O)R_{10}$, $-C(O)OR_7$, $-C(O)N(R_9)_2$, $-NR_9C(O)R_{10}$, $-C(R_{10})=NOR_7$, $-S(O)_2N(R_9)_2$, $-NR_9S(O)_2R_8$, $-N(R_9)C(O)N(R_9)_2$;

R_{A-2} is R_1 , R_2 , OR_1 , OR_2 , $N(R_{A-3})R_1$, $N(R_{A-3})R_2$, SR_1 , and SR_2 ;

R_{A-3} is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl,
 20 substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

B is a five or six-membered aromatic ring having up to 4 heteroatoms selected from $-O-$, $-N(R_{B-3})-$, $=N-$, or $-S-$;

wherein B is



25

B^1 is N, or C;

B^2 , B^3 , B^4 , and B^5 are independently N, O, S, C, provided that when valency allows, the N can have a third bond to R_{B-3} , and further provided that when valency allows, the C can have a fourth bond to R_{B-1} ;

Each R_{B-1} is independently H, halogen, alkyl, haloalkyl, substituted alkyl,
 5 cycloalkyl, halocycloalkyl, substituted cycloalkyl, alkenyl, haloalkenyl, substituted
 alkenyl, alkynyl, haloalkynyl, substituted alkynyl, heterocycloalkyl,
 haloheterocycloalkyl, substituted heterocycloalkyl, aryl, -CN, -N₃, -NO₂, -COR₁₀,
 -CO₂R₇, -CON(R₉)₂, -C(R₁₀)=NOR₇, -SCN, -OR₇, -N(R₉)₂, -SR₈, -SOR₈, -SO₂R₈,
 -SN(R₉)₂, -SON(R₉)₂, -SO₂N(R₉)₂; or

10 when two R_{B-1} are on adjacent carbon atoms, the two R_{B-1} may combine to
 form a 5-7-membered ring fused to the 5 or 6 membered ring giving a fused-bicyclic-
 ring system; wherein the 5-7-membered ring is saturated or unsaturated having up to
 two heteroatoms selected from -O-, -S-, -N(R_{B-3})-, or -N= and further having
 substitution where valency allows on the 5-7-membered ring with up to 2 substituents
 15 independently selected from R_{B-2} ;

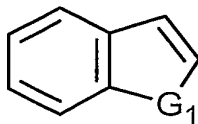
Each R_{B-2} is independently H, F, Cl, Br, I, alkyl, alkenyl, alkynyl, cycloalkyl,
 heterocycloalkyl, haloalkyl, haloalkenyl, haloalkynyl, halocycloalkyl,
 haloheterocycloalkyl, substituted alkyl, substituted alkenyl, substituted alkynyl,
 substituted cycloalkyl, substituted heterocycloalkyl, -CN, -NO₂, -OR₇, -SR₈, -S(O)₂R₈,
 20 -S(O)R₈, -OS(O)₂R₈, -N(R₉)₂, -C(O)R₁₀, -C(S)R₁₀, -C(O)₂R₇, -C(O)N(R₉)₂,
 -NR₉C(O)R₁₀, -S(O)₂N(R₉)₂, -NR₉S(O)₂R₈, -N(R₉)C(O)N(R₉)₂, or aryl;

R_{B-3} is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted
 alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl,
 substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted
 25 heterocycloalkyl, or aryl;

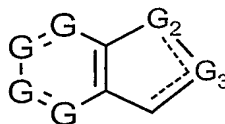
Each W^{B-1} , W^{B-2} , W^{B-3} , W^{B-4} , and W^{B-5} are independently N or CR_{B-1},
 provided that no more than 4 of W^{B-1} , W^{B-2} , W^{B-3} , W^{B-4} , or W^{B-5} are simultaneously
 N;

R_1 is a 5-membered heteroaromatic mono-cyclic moiety containing within the
 30 ring 1-3 heteroatoms independently selected from the group consisting of =N-,
 -N(R_{1-N})-, -O-, and -S-, and having 0-2 substituent selected from R_{1-1} , and further
 having 0-4 substituents independently selected from F, Cl, Br, or I;

or R_1 is a 9-membered fused-ring moiety having a 6-membered ring fused to a 5-membered ring including the formula

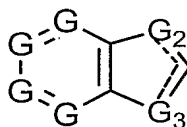


wherein G_1 is O, S or NR_{1-N} ,



5

wherein each G is independently CH , $C(R_{1-C})$, or N , and each G_2 and G_3 are independently selected from CH_2 , CH , $C(R_{1-C})$, O, S, N, and $N(R_{1-N})$, provided that both G_2 and G_3 are not simultaneously O, simultaneously S, or simultaneously O and S, or



10

wherein each G is independently CH , $C(R_{1-C})$, or N , and each G_2 and G_3 are independently selected from CH_2 , CH , $C(R_{1-C})$, O, S, N, and $N(R_{1-N})$, provided that each 9-membered fused-ring moiety has 0-1 substituent selected from R_{1-1} , and further having 0-3 substituents independently selected from F, Cl, Br, or I, wherein the R_1 moiety attaches to other substituents as defined in formula I at any position as valency allows;

15

Each R_{1-C} is independently a bond, R_{1-1} , F, Cl, Br, or I, provided that there is only one bond and further provided that R_1 can have only up to one substituent from R_{1-1} , and up to 3 substituents from halogen;

20

R_{1-N} is H, alkyl, haloalkyl, substituted alkyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, or substituted heterocycloalkyl;

R_{1-1} is alkyl, substituted alkyl, haloalkyl, $-OR_{1-2}$, $-SR_{1-2}$, $-CN$, $-NO_2$, $-N(R_{1-3})_2$;

25

Each R_{1-2} is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

Each R_{1-3} is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

R_2 is a 6-membered heteroaromatic mono-cyclic moiety containing within the ring 1-4 heteroatoms selected from =N- and having 0-1 substituent selected from R_{2-1} and 0-3 substituent(s) independently selected from F, Cl, Br, or I;

or R_2 is 10-membered heteroaromatic bi-cyclic moieties containing within one or both rings 1-3 heteroatoms selected from =N-, each 10-membered fused-ring moiety having 0-1 substituent selected from R_{2-1} and 0-3 substituent(s) independently selected from F, Cl, Br, or I, wherein the R_2 moiety attaches to other substituents as defined in formula I at any position as valency allows;

R_{2-1} is alkyl, substituted alkyl, haloalkyl, $-OR_{2-2}$, $-SR_{2-2}$, $-CN$, $-NO_2$, $-N(R_{2-3})_2$;

Each R_{2-2} is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

Each R_{2-3} is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halocycloalkyl, or haloheterocycloalkyl;

R_7 is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

R_8 is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

Each R_9 is independently H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

R_{10} is H, alkyl, haloalkyl, substituted alkyl, alkenyl, haloalkenyl, substituted alkenyl, alkynyl, haloalkynyl, substituted alkynyl, cycloalkyl, halocycloalkyl, substituted cycloalkyl, heterocycloalkyl, haloheterocycloalkyl, substituted heterocycloalkyl, or aryl;

or pharmaceutical composition, pharmaceutically acceptable salt, racemic mixture, or pure enantiomer thereof.

2. A compound of claim 1, wherein the compound has an isotopic label.
- 5 3. A compound of claim 1, wherein the compound contains a photoaffinity label wherein the compound becomes irreversibly incorporated into the nAChR upon exposure to ultraviolet light.
4. A pharmaceutical composition comprising a compound of claim 1, optionally
10 comprising another agent including an anti-psychotic agent, an agent that increases the level of ACh in the brain, an agent increasing ACh levels inhibits the activity of acetylcholinesterase or activates the production of ACh, a monoamine reuptake inhibitor, a psychostimulant, or an agent that is an alpha 7 nAChR agonist.
- 15 5. Use of a compound of claim 1 for the preparation of a medicament for treating a disease or condition in a mammal in need thereof, wherein the mammal receives symptomatic relief from activation of an alpha 7 nAChR.
6. The use of claim 5, wherein the disease or condition is cognitive and attention
20 deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), senile dementia, schizophrenia or psychosis and related cognitive deficits associated therewith, attention deficit disorder, attention deficit hyperactivity disorder, mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder,
25 traumatic brain injury, behavioral and cognitive problems associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, depression, general anxiety disorder, age-related macular degeneration, Parkinson's disease, tardive dyskinesia, Pick's disease, post traumatic stress disorder, dysregulation of food intake
30 including bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, glaucoma, neurodegeneration associated with glaucoma, or symptoms associated with pain.

7. The use of claim 6, wherein the disease or condition is attention deficit hyperactivity disorder and wherein the mammal receives symptomatic relief from the administration of at least one of a monoamine reuptake inhibitor, or psychostimulant
5 for a therapeutically effective interval, optionally wherein the psychostimulant is methylphenidate (Ritalin) administered at about 0.01 to about 0.85 mg/kg/day; dextroamphetamine (Dexedrine) administered at about 0.07 to about 0.85 mg/kg/day; amphetamine (Adderall) administered at about 0.05 to about 0.6 mg/kg/day; and pemoline (Cylert) administered at about 0.1 to about 1.6 mg/kg/day; and wherein the
10 monoamine reuptake inhibitor is desipramine (Norpramin) administered at about 0.5 to about 5.0 mg/kg/day; nortriptyline administered at about 0.1 to about 3.0 mg/kg/day; atomoxetine (Strattera) administered at about 0.1 to about 3.0 mg/kg/day; reboxetine administered at about 0.03 to about 3.0 mg/kg/day; fluoxetine (Prozac) at about 0.2 to about 20 mg/kg/day; tomoxetine administered at about at about 0.1 to
15 about 1.1 mg/kg/day; bupropion (Wellbutrin) administered at about at about 1.0 to about 1.1 mg/kg/day; and modafonil (Provigil) administered at about at about 1.0 to about 5.7 mg/kg/day.

8. The use of claim 5, wherein the mammal receives therapeutic relief from the
20 administration of an agent that inhibits the activity of acetylcholinesterase; wherein the agent inhibiting acetylcholinesterase is optionally Aricept and Reminyl.

9. The use of claim 5, wherein the mammal receives therapeutic relief from the administration of an agent that is ACh or that increases levels of ACh in the brain, optionally ACh or a nutritional supplement.
25

10. The use of a compound of claim 1 for the preparation of a medicament for treating a disease or condition in a mammal in need thereof, wherein the mammal receives symptomatic relief from decreasing the level of TNF- α .

11. The use of claim 10, wherein the symptomatic relief would be to treat the
30 mammal for pain, inflammation, cancer, or diabetes.

12. Use of a compound of claim 1 for the preparation of a medicament for treating a disease or condition in a mammal in need thereof, wherein the mammal receives

symptomatic relief from increasing vascular angiogenesis, optionally wherein the disease or condition is wound healing, healing bone fracture, ischemic heart disease, or stable angina pectoris.

- 5 13. Use of a detectably labeled compound of claim 2 for the preparation of composition for diagnosing disease in a mammal, comprising administering to the composition and detecting the binding of that compound to an alpha 7 nAChR, optionally using position emission topography or single-photon emission computed tomography.
- 10 14. The use of claim 13, wherein the disease is Alzheimer's disease, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), senile dementia, Parkinson's disease, schizophrenia, psychosis, attention deficit disorder, attention deficit hyperactivity disorder, depression, anxiety, general anxiety disorder, post traumatic stress disorder,
- 15 mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems in general and associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, tardive dyskinesia, Pick's disease, dysregulation of food intake including bulimia and
- 20 anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, age-related macular degeneration, glaucoma, neurodegeneration associated with glaucoma, diabetic retinopathy, or symptoms associated with pain.

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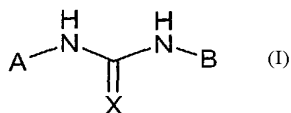
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(54) Title: POSITIVE ALLOSTERIC MODULATORS OF THE NICOTINIC ACETYLCHOLINE RECEPTOR



(57) Abstract: The invention provides compounds of Formula (I). These compounds may be in the form of pharmaceutical salts or compositions, may be in pure enantiomeric form or racemic mixtures, and are useful in pharmaceuticals used to treat diseases or conditions in which $\alpha 7$ nAChR is known to be involved.



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International Application No
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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/24785 A (KATO MASAYUKI ; NODA YUKA (JP); SPEARS GLEN W (JP); HARADA KEIKO (JP);) 11 June 1998 (1998-06-11) examples 1,3-11,27-31,36-43,45,49,51 -----	1,6
X	WO 99/09024 A (JOHNS AMANDA ; PORTER RODERICK ALAN (GB); SMITHKLINE BEECHAM PLC (GB);) 25 February 1999 (1999-02-25) page 1 - page 2; example 35 -----	1,6
X	WO 99/14197 A (THOMPSON MERVYN ; PORTER RODERICK ALAN (GB); SMITHKLINE BEECHAM PLC (G) 25 March 1999 (1999-03-25) claim 7; example 54 -----	1,6
X	WO 99/24035 A (SQUIBB BRISTOL MYERS CO) 20 May 1999 (1999-05-20) page 66; example 92 ----- -/-	1

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☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/32106 A (BAYER AG) 1 July 1999 (1999-07-01) examples C2a-2, C2b-2, C2c, C3a, C3b, C4b, C4c, D9-2; table 1: 11, 12, 15, 21, 37, 42...; table 2: 180, 182-184, 186-188...; table 3: 292, 298, 299...; table 4: 341, 346-352...; table 5: 376, 380, 387... -----	1
X	WO 99/32110 A (BAYER AG) 1 July 1999 (1999-07-01) examples D4 and table 1: 32-37 -----	1
X	WO 99/32111 A (BAYER AG) 1 July 1999 (1999-07-01) examples C2a-2, C2b-2, C2c, C3a, C3b, C4a, C4b, C4c, D9-1, D 9-2 and tables 1-5 -----	1
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X	WO 02/062763 A (RIEDL BERND ; LOWINGER TIMOTHY B (JP); DUMAS JACQUES (US); RENICK JOEL) 15 August 2002 (2002-08-15) example C5; table 7: Nos 107-110, 112 -----	1
X	WO 02/085857 A (RIEDL BERND ; LOWINGER TIMOTHY B (DE); HATOUM-MOKDAD HOLIA (US); DUMAS) 31 October 2002 (2002-10-31) examples B4; table 1: Nos 10-12; table 2: No 2; table 3: Nos 25-27; table 4: No 28 -----	1
X	WO 03/022852 A (ROCHER JEAN-PHILIPPE ; GLAXOSMITHKLINE K K (JP); NAKANO MASATO (JP); S) 20 March 2003 (2003-03-20) examples 292, 307 -----	1
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE; ABDEL-RAHMAN, R. M.: "Some reactions of 3-thioxo-6-'2-acyl/alkyl aminophenyl!-1,2,4- triazin-5(2H,4H)-ones" XP002302410 retrieved from STN Database accession no. 1991:607959 CAS RN 136715-95-2 abstract & PAKISTAN JOURNAL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, vol. 33, no. 12, 1990, pages 520-524, -----</p>	1
X	<p>DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE; 1 January 2004 (2004-01-01), XP002302411 Database accession no. 2004:533495 CAS RN 266692-00-6 the whole document -----</p>	1
X	<p>DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1988, XP002302412 Beilstein Registry Number 29952 the whole document & CHEM. BER., vol. 80, 1947, page 143, -----</p>	1
X	<p>BUNNETT, J. F. ET AL: "Homocyclic ring closures via benzyne intermediates. A new synthesis of 1-substituted benzocyclobutenes" JOURNAL OF ORGANIC CHEMISTRY, vol. 27, 1962, pages 3836-3843, XP002302407 page 3839, column 1 -----</p>	1
X	<p>DUNCAN, ROBERT L., JR. ET AL: "Synthesis of indolo- and benzimidazoquinazolines and benzodiazepines" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 10, no. 1, 1973, pages 65-70, XP002302408 example 35; table IV -----</p>	1
X	<p>CH 554 876 A (PFIZER) 15 October 1974 (1974-10-15) example XXXII -----</p>	1
X	<p>US 3 707 560 A (ANGELIS GERALD GEORGE DE ET AL) 26 December 1972 (1972-12-26) column 27 - column 28; example XXXVIII -----</p>	1
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/000838

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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